Supplementary Information (SI) for Catalysis Science & Technology.

Exploring pre-catalyst scope and selectivity in Negishi coupling of aryl iodides in deep eutectic solvents

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Supporting Information

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Experimental Details

General methods

All reagents were purchased from commercial sources unless their preparation is described. THF was dried by refluxing over sodium wire for 3 days prior to distillation and was then stored over 4 Å molecular sieves. Water content was confirmed to be lower than 10 ppm by Karl Fischer analysis. Anhydrous $ZnCl_2$, Zn^0, LiCl and $Pd(OAc)_2(PPh_3)_2$ were stored in a dinitrogen-filled glovebox and used without further purification.

For the synthesis of the electrophiles, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL EXC400 spectrometer (operating at 400 MHz for ^{1}H and 100.5 MHz for ^{13}C) or Bruker AVANCE III 500 (operating at 500.23 MHz for ^{1}H and 125.77 MHz for ^{13}C). For the analysis of the mono-substituted cross-coupling product of methyl 2,3,5-trisubstituted benzoate and benzyl zinc, a 600 MHz Bruker Avance III HD spectrometer equipped with a room temperature broadband probe was used (operating at 600 MHz for ^{1}H and 150 MHz for ^{13}C). All chemical shifts were reported in parts per million and were referenced using the chemical shifts of residual protio solvent resonances to internal solvent peaks. The chemical shifts are consecutively reported as position (δ), relative integral, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad,), coupling constant (*J* in Hz) and assignment. Gas chromatography experiments were performed on a ThermoScientific Trace 1300 GC equipped with 2 columns: a) DB5 general purpose column, nonpolar (5% Phenyl)methylpolysiloxane (30 cm x 0.25 mm x 0.25μm) and b) Rxi-17 mid polarity column (50% Phenyl)methylpolysiloxane (30 cm x 0.25 mm x 0.25μm); autosampler, detector: FID, carrier gas: Hydrogen, samples diluted in CH_2Cl_2. Method: Run time between 15 and 21 min, splitless injections at 280 ^{o}C, column flow 1.5 mL/mim. Ramp: Starting temperature: 50 ^{o}C held for 0.5 min, then ramped at 100 ^{o}C/min to 90 ^{o}C, then ramped at 15 ^{o}C/min to 300 ^{o}C, held for 6 min. FID: 330 ^{o}C. GC-MS experiments were performed on a JEOL AccuTOF GCx plus mass spectrometer, GC: Agilent 7890B GC, ionization method: EI.

Preparation of DESs

Choline chloride was recrystallized from ethanol in a Schlenk tube, the solvent was removed by cannula filtration and the crystals dried under vacuum. The amides and polyols were dried under vacuum at 100 ^{o}C for 30 minutes. Acetyl choline chloride was used as purchased. For all DESs, the components were added to a round-bottom flask at the corresponding stoichiometries shown in Table S1, stirred and heated to 80 ^{o}C for 30 minutes or until a homogeneous liquid was formed. For the dry-DESs, the components were added to an oven-dried Schlenk tube using protecting N_2 atmosphere before being heated and stirred, as above. The water content was measured through coulometric analysis using a Mettler Toledo C20S Coulometric Karl Fisher titrator. Synthesised DES's were stored in a sealed flask.

Table S1: Employed DES and their water content

Entry	DES	Ammonium Salt	Hydrogen Bond Donor	NR_4X/HBD Stoichiometry	Water (ppm)	χ_{H2O} (%)
1	ChCl/Urea	ChCl	Urea	1:2	28571[a], 382[b]	29.7, 0.5
2	ChCl/Gly	ChCl	Glycerol	1:2	24720[a], 317[b]	31.3, 0.6
3	ChCl/DMU	ChCl	Dimethylurea	1:2	46535[a]	46.0
4	ChCl/$AcNH_2$	ChCl	Acetamide	1:2	10420[a]	13.1
5	AcChCl/Urea	AcChCl	Urea	1:1	-	-

[a] Water content reported for DES equilibrated in a sealed flask with the lab atmosphere for a week.

[b] DES stored under N_2 atmosphere.

Preparation of Zn reagents

n-butylzinc chloride and benzyl zinc bromide were prepared in house for these experiments, all other alkylzinc reagents were purchased from commercial suppliers as 0.5 M solutions in THF.

n-Butylzinc chloride (**a**): In an oven-dried Schlenk tube under nitrogen atmosphere, $ZnCl_2$ (138 mg, 1.0 mmol) was dissolved in 1 mL of anhydrous THF. The mixture was cooled to -78 ^oC with a dry ice/acetone bath and a solution of *n*-butyllithium 2.5 M in hexanes (titrated prior to use to determine molarity using an established procedure [1]) was added dropwise (0.4 mL, 1.0 mmol). The mixture was stirred for 30 minutes at -78 ^oC and then allowed to reach room temperature for 30 min before its usage. The reagent was employed without further characterization.

Benzylzinc bromide (**b**): Prepared according to literature method.[2, 3] An oven-dried Schlenk tube under nitrogen atmosphere was loaded with Zn^0 powder (325 mesh) (1.34g, 21 mmol) and 2 mL of dry THF. In a second oven-dried Schlenk tube benzyl bromide freshly distilled under nitrogen (1.7 mL, 14 mmol) was dissolved in 7 mL of dry THF. The Zn mixture was cooled to 0 ^oC and the benzyl bromide solution was added dropwise with a rate of 1 drop per 10 seconds. After the addition, the reaction was stirred for 18 hours at 0 ^oC under nitrogen. Finally, the excess of Zn was decanted, and the benzyl zinc bromide solution filtered and stored in an ampule at 4 ^oC. The organozinc solution was titrated by dissolving I_2 (127 mg, 0.5 mmol) in a previously prepared anhydrous solution of LiCl in THF 0.5 M (2 mL). The titration was carried out in an ice bath. The equivalence point was reached when the iodine mixture became colourless. The reagent was employed without further characterization.

Preparation of *ortho*-coordinating electrophiles

<u>N’N-diethyl-2-iodobenzamide</u>: This product was prepared according to a literature method with slight modifications.[4] Reaction conditions: 2-iodobenzoic acid (2 g, 8.1 mmol, 1 equivalent) was placed into an oven-dried two-neck round-bottom flask equipped with a magnetic stirred bar under N_2 atmosphere. The acid was dissolved in 16 mL of dry CH_2Cl_2 (0.5 M solution) and 5 drops of dry dimethylformamide. Then, the reaction mixture was cooled to 0 °C and oxalyl chloride (820 µL, 9.7 mmol, 1.2 equivalents) was added dropwise. Gas evolution was observed. Afterwards, the reaction was allowed to reach room temperature and stirred for 3 hours. After this, the solvent removed under vacuum and the crude redissolved in 16 mL of dry CH_2Cl_2. The reaction mixture was cooled to 0 °C and diethylamine (3.3 mL, 32.24 mmol. 4 equivalents) was added dropwise. The reaction was allowed to reach room temperature and stirred for 3 h. Work up: The reaction was quenched with 16 mL of deionised water. The aqueous phase was extracted CH_2Cl_2 (2 x 10 mL) and the organic phases as well as the initial reaction solvent combined and washed with HCl 1M (2 x 10 mL) and brine (1 x 15 mL). The crude was concentrated under vacuum and purified by column chromatography (SiO_2 44 g, Hexane/Ethyl acetate 3:2). A yellow transparent oil was obtained 88% yield.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (dd, *J* = 1.0, 8.1 Hz, 1H, (4)), 7.36 (td, *J* = 1.2, 7.6 Hz, 1H, (2)), 7.19 (dd, *J* = 1.7, 7.6 Hz, 1H, (1)), 7.04 (td, *J* = 1.7, 7.7 Hz, 1H, (3)), 3.86 (m, 1H), 3.28 (m, 1H) 3.13 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H).

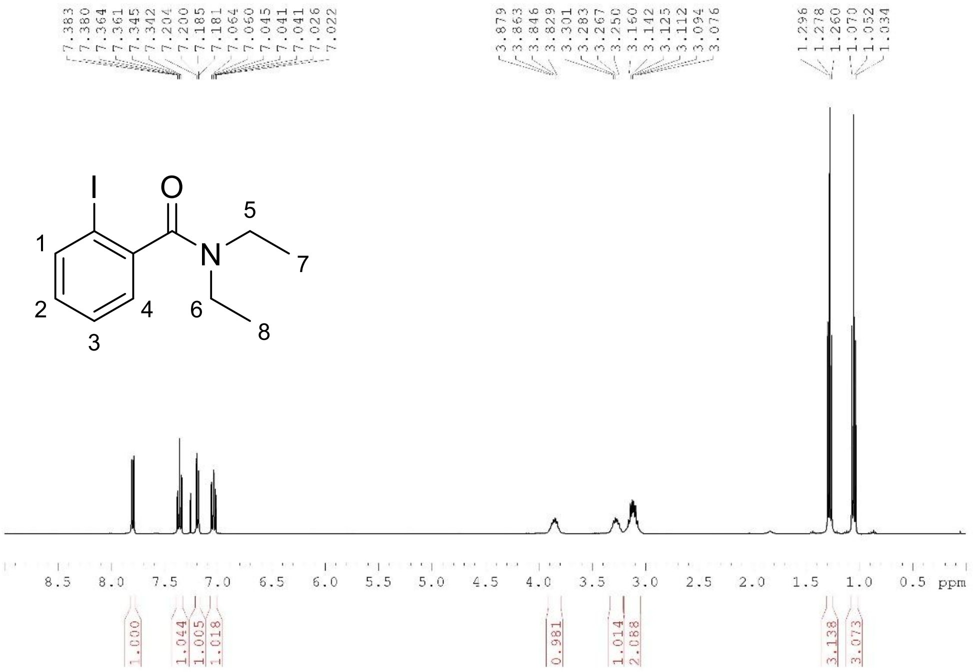


Figure S1: ^1H NMR spectrum of N’N-diethyl-2-iodobenzamide

2-Iodobenzanilide**:** Prepared according to literature method with slight modifications.[4] Reaction conditions: 2-iodobenzoic acid (4 g, 0.016 mol, 1 equivalent) was placed was placed into an oven-dried two-neck round-bottom flask equipped with a magnetic stirred bar under N_2 atmosphere. The acid was dissolved in 30 mL of dry CH_2Cl_2 (0.5 M solution), 10 drops of dry dimethylformamide were added. Then, the reaction mixture was cooled to 0 °C and oxalyl chloride (1.640 mL, 0.019 mol, 1.2 equivalents) was added dropwise. Gas evolution was observed. Afterwards, the reaction was allowed to reach room temperature and stirred for 3 hours. After this, the solvent was removed under vacuum and the crude redissolved in 30 mL of dry CH_2Cl_2. The reaction mixture was cooled to 0 °C and aniline (5.9 mL, 0.064 mol 4 equivalents) was added dropwise. The reaction was allowed to reach room temperature and stirred for 3h. Work up: The reaction was quenched with 30 mL of deionised water. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases were washed with HCl 1M (2 x 10 mL) and brine (1 x 15 mL). The crude was concentrated under vacuum and purified by recrystallization from boiling CH_2Cl_2, white needles were obtained, 69% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (dd *J* = 0.8, 8.1 Hz, 1H (4)), 7.74 (s, 1H, (55)), 7.62 (m, 2H, (6 & 10)), 7.45 (dd, *J* = 1.6, 7.6 Hz, 1H, (1)), 7.37 (m, 3H, (2, 7 & 9)), 7.16 (tt, *J* = 1.7, 7.7 Hz, 1H (8)), 7.11 (td, 1.7, 7.7, 1H, (3)).

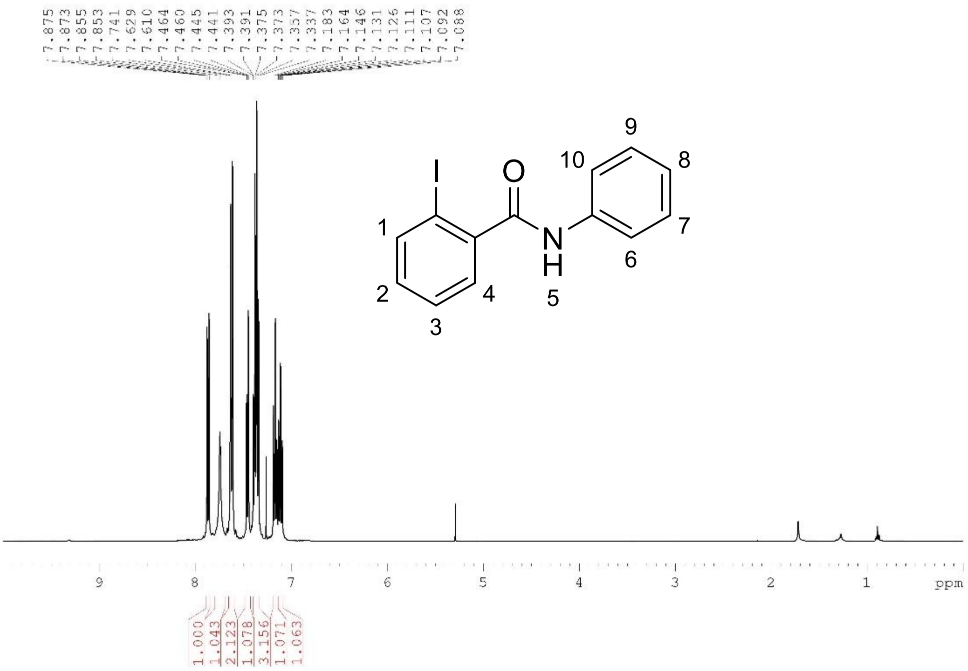


Figure S2: ^{1}H NMR spectrum of 2-iodobenzanilide

2-(2-iodophenyl)pyridine**:** Prepared according to literature method with slight modifications.[5] Reaction conditions: 2-phenylpiridine (2.55 mL, 2.761 g, 0.0178 mol), *N*-iodosuccinimide (8 g, 0.0178 mol) and $Pd(OAc)_2$ (200 mg 0.00089 mol) were added to a 250 mL round bottom flask and dissolved in 175 mL of acetonitrile to achieve a 0.1M concentration of pyridine. A condenser was settled and the reaction stirred at 100°C for three days. A purple-pink heterogeneous mixture was obtained. The acetonitrile was removed under vacuum, and the product purified by flash column chromatography. First, the purple non-polar impurities were removed with hexanes as eluent and then the product was separated from the starting material using 10% EtOAc in hexanes as eluent. A yellow oil was obtained, yield 35%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.70 (dq, *J* = 0.9, 5.0 Hz, 1H, (1)), 7.98 (dd, *J* = 1.1, 8.0 Hz, 1H, (5)), 7.76 (td, *J* = 1.8, 7.8 Hz, 1H, (3)), 7.50 (dt, *J* = 1.1, 7.9 Hz, 1H (4)), 7.46 (dd, *J* = 2.2, 7.7 Hz, 1H, (8)), 7.43 (td, *J* = 1.1, 7.8 Hz, 1H, (7)), 7.32 (ddd, *J* = 1.1, 5.0, 7.7 Hz, 1H, (2)), 7.08 (ddd, *J* = 2.2, 6.4, 8.0 Hz, 1H (6)).

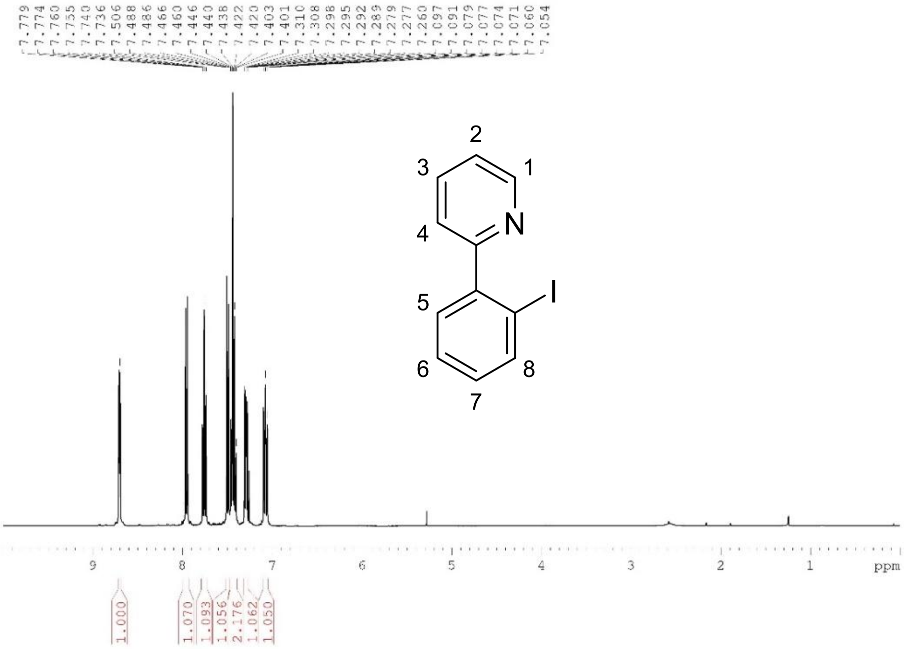


Figure S3: ^{1}H NMR spectrum of 2-(2-iodophenyl)pyridine

1-iodo-2-(methoxymethyl)benzene**:** Prepared according to literature method with slight modifications.[6] Reaction conditions: The synthesis was carried out under inert atmosphere. In an oven-dried Schlenk tube, NaH (492 mg, 20.5 mmol) was dissolved in 15 mL of dry THF. In a second oven-dried Schlenk tube, a solution of 2-iodobenzyl alcohol (4g, 17 mmol) in 15 mL of dry THF was prepared. The iodoarene solution was then added dropwise to the NaH solution at 0 °C. Afterwards, the reaction mixture was stirred for 0.5 h at 0 °C. After this, iodomethane (1.3 mL, 21 mmol) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was then stirred for 4 h and allowed to reach room temperature gradually during this period. Work-up: The reaction was quenched with 30 mL of deionized water; the aqueous mixture was extracted with CH_2Cl_2 (3 x 20 mL). Then, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by column chromatography, eluent: 10% EtOAc in hexane. A colourless oil was obtained, 85% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (dd, *J* = 1.2, 7.9 Hz, 1H, (1)), 7.42 (dd, *J* = 1.7, 7.6 Hz, 1H, (4)), 7.35 (td, *J* = 1.2, 7.4 Hz, 1H, (3)), 6.99 (dt, *J* = 1.8, 7.55 Hz, 1H, (2)), 4.45 (s, 2H (5)), 3.47 (s, 3H, (6))

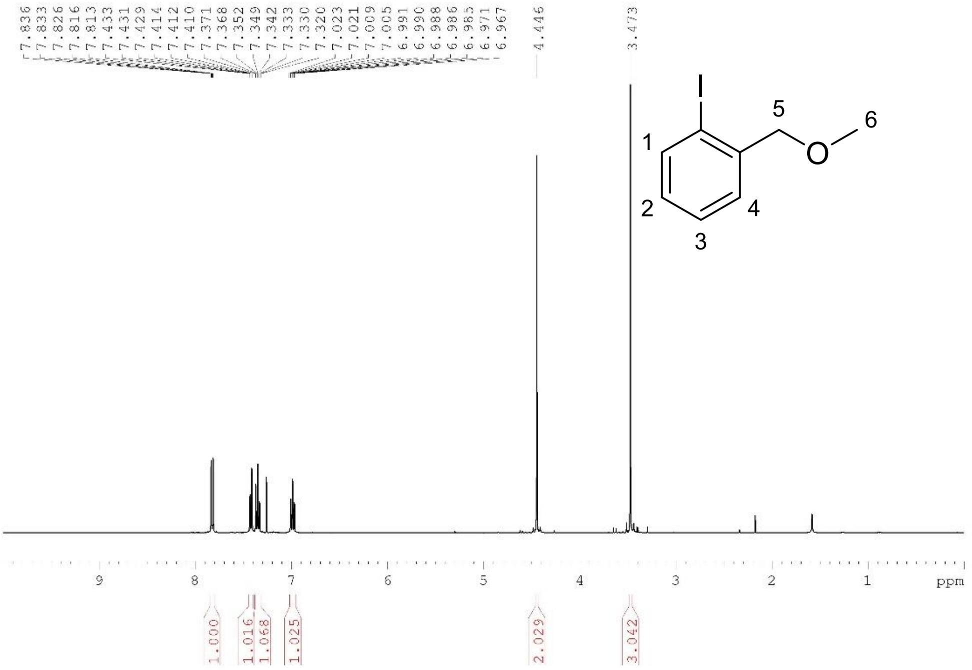
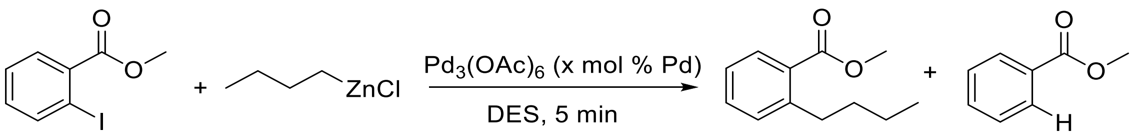


Figure S4: ^{1}H NMR spectrum of 1-iodo-2-(methoxymethyl)benzene

Procedure for initial optimisation experiments (manuscript Table 1)



Scheme S1: Model Negishi coupling reaction chosen to adapt in DESs.

In a typical experiment, a round-bottom flask was loaded with $Pd_3(OAc)_6$ (4.5 mg, 2 mol% Pd) and 5 mL of the respective DES, the mixture was heated to the desired temperature and stirred at 1000 rpm until the mixture became orange (around 10 minutes). After palladium had been solubilized, the respective iodoarene (0.5 mmol) was added and mixed for 10 minutes. Then, the organozinc solution was added in either a single, fast addition or dropwise (1 drop every 3 seconds approximately) to the Pd/arene mixture while stirring at 1000 rpm. The reaction mixture was stirred for 5 min at the desired temperature. Then, it was quenched with 15 mL of 2M aqueous solution of ammonium chloride, extracted with CH_2Cl_2 (3 x 15 mL), washed with 30 mL of deionized water and 30 mL of brine, dried over $MgSO_4$ and filtered. The crude product was concentrated on a rotary evaporator under reduced pressure and weighed. The crude product was then analysed by ^1H NMR spectroscopy. The conversion was calculated by integration of the characteristic proton signals from the methyl groups on the ester functionality of the product, the aryl halide and the dehalogenated side-product. The reaction mixtures from the experiments performed in ChCl/DMU and ChCl/$AcNH_2$ DESs were analysed by GC (as described below).

This section shows the full set of results from the optimisation of the reaction conditions of the Negishi coupling between methyl-2-iodobenzonate and *n*-butylzinc, Scheme S1. Table 1 in the main section shows selected results from key reactions.

^1H NMR characterization of **2a**: ($CDCl_3$, 400 MHz). δ 7.86 (dd, *J* = 1.1, 7.8 Hz, 1H, (9)), 7.41 (td, *J* = 1.2, 7.5 Hz, 1H, (8)), 7.25 (m, 2H, (7, 8)), 3.90 (s, 3H, (4)), 2.96 (t, *J* = 7.7 Hz, 2H, (5)), 1.59 (quintet, *J* = 7.7 Hz, 2H, (3)), 1.40 (sextet, *J* = 7.4 Hz, 2H, (2)), 0.95 (t, *J* = 7.3 Hz, 3H).

Table S2: Full optimisation results for reaction in Scheme S1.

Entry	Solvent	Solvent wet/dry	Temp. (°C)	[Pd] (mol %)	^{n}BuZnCl (equiv.)	RZnCl rate of addition	Conv. to **2a** (%)	Conv. to **3** (%)
1[a]	ChCl/G	wet	40	0.5	2.0	dropwise	6	0
2[a,c,d]	ChCl/G	wet	40	0.5	2.0	dropwise	0	0
3[a,d]	ChCl/G	dry	40	1	1.6	dropwise	0	0
4[a]	ChCl/U	dry	40	1	1.6	dropwise	88	10
5[a]	ChCl/U	dry	40	2	1.6	dropwise	90	6
6[a]	ChCl/U	dry	40	2	2.0	fast, single	31	10
7.1	ChCl/U	wet	40	1	1.6	dropwise	27	3
7.2	ChCl/U	wet	40	1	1.6	dropwise	20	2
8	ChCl/U	wet	40	1	2.0	fast, single	46	8
9	ChCl/U	wet	40	2	2.0	dropwise	55	5
10	ChCl/U	wet	40	2	2.0	fast, single	46	8
11	ChCl/U	wet	50	2	2.0	dropwise	58	7
12[a]	ChCl/U	dry	60	1	2.0	dropwise	87	12
13.1	ChCl/U	wet	60	1	2.0	dropwise	80	5
13.2	ChCl/U	wet	60	1	2.0	dropwise	40	4
13.3	ChCl/U	wet	60	1	2.0	dropwise	38	4
13.4	ChCl/U	wet	60	1	2.0	dropwise	51	6
13.5	ChCl/U	wet	60	1	2.0	dropwise	87	12
14.1	ChCl/U	wet	60	2	2.0	dropwise	97	0
14.2	ChCl/U	wet	60	2	2.0	dropwise	90	10
14.3	ChCl/U	wet	60	2	2.0	dropwise	77	8
14.4	ChCl/U	wet	60	2	2.0	dropwise	80	8
14.5	ChCl/U	wet	60	2	2.0	dropwise	78	5
14.6	ChCl/U	wet	60	2	2.0	dropwise	91	8
15[e]	ChCl/U	wet	60	2	2.0	dropwise	80	-
16	ChCl/U	wet	60	2	2.0	fast, single	70	7
17[f]	ChCl/U	wet	60	2	2.0	dropwise	68	4
18[g]	ChCl/U	wet	60	2	2.0	dropwise	25	3
19[a,b]	THF	dry	40	2	2.0	dropwise	84	1
20[h]	ChCl/DMU	wet	80	2	1.5	dropwise	14	1
21[h]	ChCl/AcNH$_2$	wet	80	2	1.5	dropwise	14	1
22[i]	ChCl/U	wet	60	2	2.0	dropwise	0	0
23[j]	ChCl/U	wet	60	2	2.0	dropwise	0	0

[a] Schlenk line and protective N_2 atmosphere used. [b] [Bu$_4$N]Br added as additive. [c] 10 cm^3 of DES. [d] Reaction mixture stirred for 12 hours [e] Isolated yield after purification by column chromatography. [f] With PdCl$_2$. [g] With Pd(PPh$_3$)$_4$. [h] Conversion determined by GC using a DB5 column. [i] In the absence of Pd. [j] In the absence of ^{n}BuZnCl, reaction time 12 h.

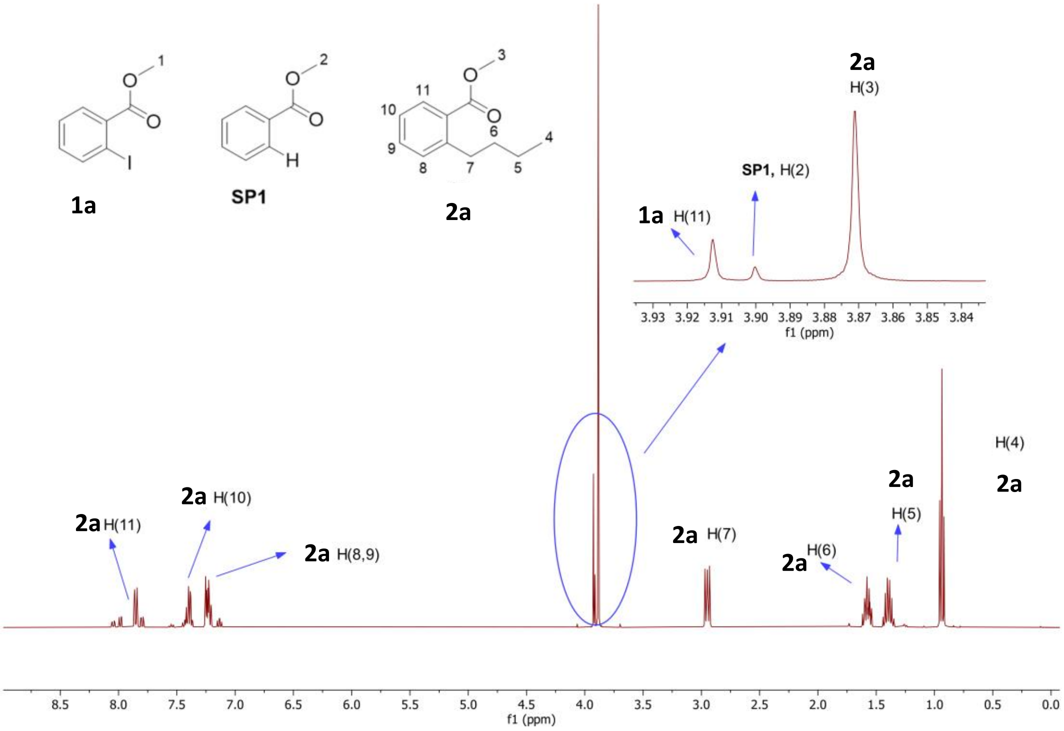


Figure S5: Example of a ^{1}H NMR spectrum of the worked-up reaction mixture for the reaction between methyl 2-iodobenzoate and *n*-butylzinc chloride showcasing the peaks used to determine the ratio between starting material, coupling product and dehalogenation product.

Catalyst re-use experiments

The re-use of the DES/Pd mixture was tested by extracting the organic products and unreacted starting material directly from the DES using dichloromethane. The results showed a decrease in conversion to **3a** from 83% for the first cycle, to 64% for the second and 56% after a third cycle. More details are given below.

A round-bottom flask was loaded with $Pd_3(OAc)_6$ (11.23 mg, 5 mol %), methyl 2-iodobenzoate (147 µL, 1 mmol, 1 equivalent) and 5 mL of ChCl/Urea DES, the mixture was heated to 60 ^oC and stirred at 1000 rpm until reaction becomes orange (around 10 minutes). Then, a solution of *n*-butylzinc chloride in dry THF (2 mmol, 2 equivalents) prepared as described previously was added dropwise (1 drop every 3 seconds approximately) while stirring at 1000 rpm. The reaction mixture was stirred for 5 min at the 60 ^oC. Then, the products were extracted from ChCl/Urea DESs with dichloromethane (5 x 10mL) by adding the solvent directly to the round-bottom flask and stirring vigorously for a minute and decanting the dichloromethane. All the organic phases were collected, dried over $MgSO_4$ and concentrated under vacuum. The remaining organic solvent was removed from the DES by heating under vacuum. The reaction mixture was reloaded with methyl 2-iodobenzoate and the procedure repeated two more times. Hexamethylbenzene was added to the crude reaction mixtures as an internal standard and the crude was analysed by ^{1}H NMR spectroscopy to determine conversion.

Table S11: Negishi coupling recycling experiment

Entry	Analyte	Integral Analyte	Integral Std	NMR Conversion (%)	Cycle
1	CC-Product	2.98	1.93	80	Cycle1
2	Dehalogenated	0.74	1.93	14	Cycle1
3	Starting Material	0.04	1.93	1	Cycle1
4	CC-Product	2.88	2.27	64	Cycle2
5	Dehalogenated	0.74	2.27	12	Cycle2
6	Starting Material	0.47	2.27	14	Cycle2
7	CC-Product	3.01	2.43	56	Cycle3
8	Dehalogenated	0.59	2.43	8	Cycle3
9	Starting Material	1.36	2.43	34	Cycle3

Conversion determined by ^{1}H NMR with hexamethylbenzene as internal standard.

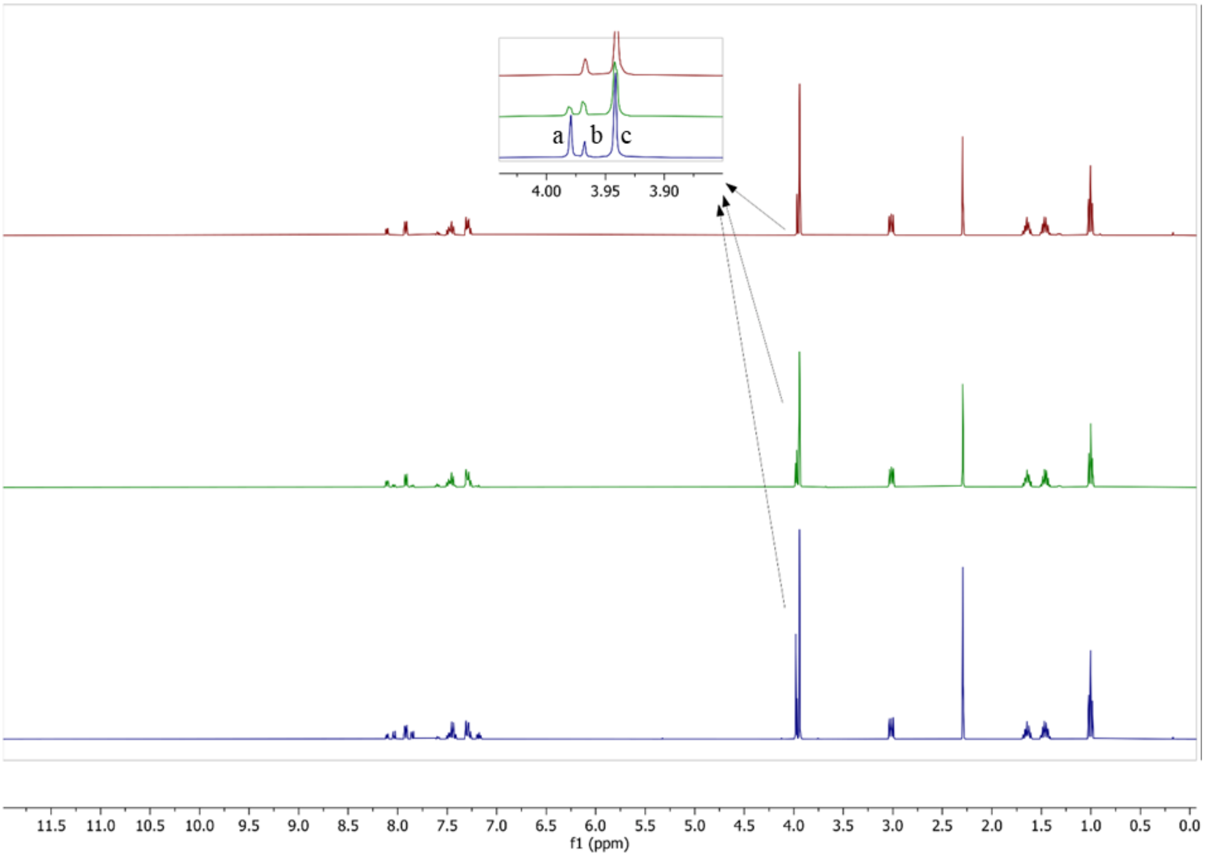
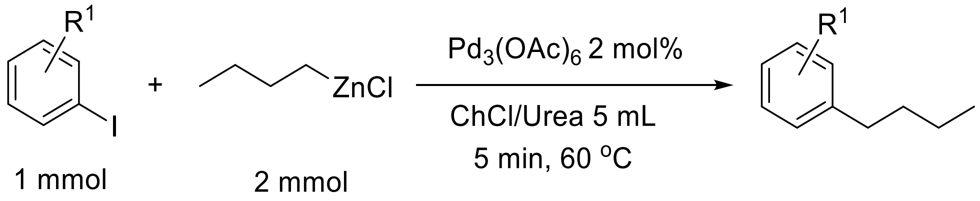
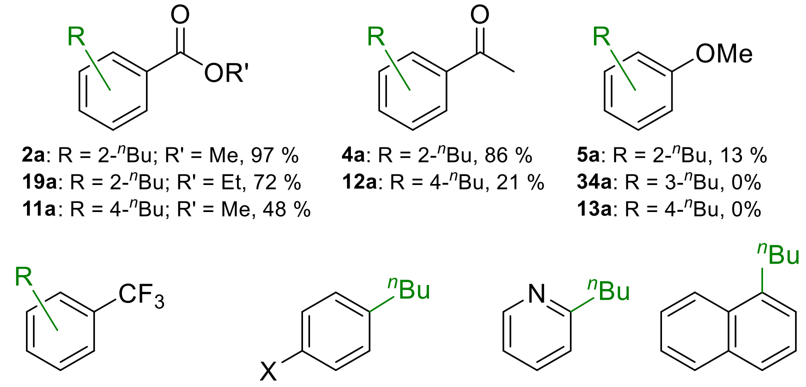


Figure S20: Stacked ^{1}H NMR spectra from the Negishi coupling recycling experiments between methyl 2-iodobenzoate and *n*-butylzinc chloride catalysed by Pd acetate in DES. Red: first cycle, green: second cycle, blue: third cycle. a) Methyl peak from starting material, b) methyl peak from dehalogenated side product, c) methyl peak from cross-coupling product.

Procedure for initial substrate scope experiments



Scheme S2: Negishi cross-couplings between *n*-butylzinc chloride and a series of electrophiles bearing electron-withdrawing or electron-donating functional groups.



2a: R = 2-^{n}Bu; R' = Me, 97 %
19a: R = 2-^{n}Bu; R' = Et, 72 %
11a: R = 4-^{n}Bu; R' = Me, 48 %

4a: R = 2-^{n}Bu, 86 %
12a: R = 4-^{n}Bu, 21 %

5a: R = 2-^{n}Bu, 13 %
34a: R = 3-^{n}Bu, 0%
13a: R = 4-^{n}Bu, 0%

37a: R = 2-^{n}Bu, 0 %
38a: R = 3-^{n}Bu, 5 %
39a: R = 4-^{n}Bu, 0%

7a: R = ^{n}Bu; X = H; 61 %
14a: R = ^{n}Bu; X = NO_2; 32 %
15a: R = ^{n}Bu; X = Me; 0%
40a: R = ^{n}Bu; X = Cl; 10 %

41a: 0%

16a: 4 %

Scheme S3: Preliminary substrate scope. Reaction conditions: **a** (2 mmol) in 2 cm^3 dry THF was added slowly to ArI (1 mmol) and $Pd_3(OAc)_6$ (2 mol % Pd; except for **4a**, where 5 mol %) in 5 cm^3 "wet" ChCl/urea at 60 °C.

A round-bottom flask was loaded with $Pd_3(OAc)_6$ (4.5 mg, 2 mol % Pd) and 5 mL of ChCl/Urea DES, the mixture was heated to 60 °C and stirred at 1000 rpm until reaction became orange (around 10 minutes). After the palladium had been solubilized, the respective iodoarene (1.0 mmol) was added and mixed for 10 minutes. After this, *n*-butylzinc chloride was added in a dropwise fashion (1 drop every 3 seconds approximately) to the Pd/arene mixture while stirring at 1000 rpm. The reaction mixture was stirred for 5 min at 60 °C. Then, quenched with 15 mL of 2M aqueous solution of ammonium chloride, extracted with CH_2Cl_2 (3 x 15 mL), washed with 30 mL of deionized water and 30 mL of brine, dried over $MgSO_4$ and filtered. The reaction mixture was analysed by GC (as described below).

Table S3: Results for initial substrate scope experiments along with the reference compound used for GC studies (as described below).

Entry	Electrophile	GC reference compound used	Ar-^{n}Bu Conv. (%)	Ar-H Conv. (%)	Ar-I Recov. (%)
1[a]	4-Bromoanisole	4-Bromoanisole	0	-	100
2[b]	Bromobenzene	Bromobenzene	0	-	100
3[b]	Iodobenzene	Iodobenzene	62	-	38
4[b]	4-Chloro-1-iodobenzene	4-Chloro-1-iodobenzene	10	-	68
5[b]	2-Iodoanisole	Anisole	5		85
6[b]	Ethyl-2-iodobenzoate	Methyl benzoate	72	9	19
7[a]	Methyl 2-iodobenzoate	-	97	3	0
8[c]	Methyl-4-benzoate	-	48	15	17
9[a]	1-Iodonaphthalene	Naphthalene	4	4	92
10[a]	3-Iodoanisole	3-Iodoanisole	0	0	100
11[b]	4-Iodoacetophenone	Acetophenone	21	8	71
12[a,d]	2-iodoacetophenone	Acetophenone	86	1	11
12[b]	4-Iodotoluene	Naphthalene	0	-	94
13[a]	4-Iodonitrobenzene	4-Iodonitrobenzene	32	8	45
14[b]	4-Iodobenzotrifluoride	4-Iodobenzotrifluoride	0	-	100
15[b]	2-Iodopyridine	2-Iodopyridine	0	-	100
16[b]	2-Iodobenzotrifluoride	2-Iodobenzotrifluoride	0	-	100
17[a]	3-Iodobenzotrifluoride	3-Iodobenzotrifluoride	0	-	75

Conversions obtained by GC analysis of the reaction products using a DB-5 column. [a] Decane was used as internal standard. [b] Naphthalene was used as internal standard. [c] Conversion determined by ^{1}H-NMR. [d] $Pd_3(OAc)_6$ 5 mol % Pd.

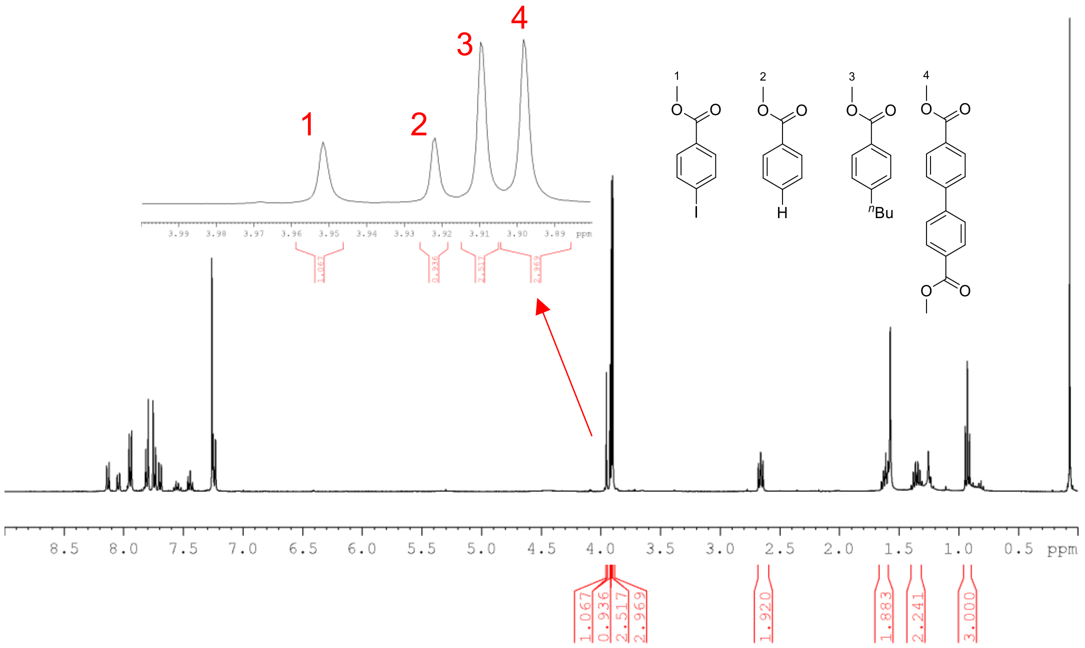


Figure S6: Table S3 entry 8 ^{1}H NMR spectrum displaying the peaks taken as references to determine the ratio between starting material, productive coupling product, dehalogenation product and homocoupling product.

Final procedures for coupling of iodoarenes (manuscript scheme 4)

A round-bottom flask was loaded with either $Pd_3(OAc)_6$ (5.5 mg, 5 mol % Pd), $Pd(OAc)_2(PPh_3)_2$ (18.7 mg, 5 mol%) or $Pd(P^tBu_3)_2$ (12.8 mg, 5 mol%) and 5 mL of ChCl/Urea DES. The mixture was heated to 60 °C and stirred vigorously until the mixture became orange (around 10 minutes). For reactions with 3-iodobenzoate and 4-iodobenzoate, the iodoarene was also added (0.5 mmol). For all other iodoarenes, the respective iodoarene (0.5 mmol) was added after 10 mins and stirred for a further 10 minutes. After this, the respective organozinc reagent was added in a dropwise fashion (1 drop every 3 seconds approximately). The reaction mixture was stirred at 60 °C for 5 minutes, then quenched with 15 mL of a 2M solution of ammonium chloride, extracted with CH_2Cl_2 (3 x 15mL), washed with 30 mL of deionized water and 30 mL of brine, dried over $MgSO_4$ and filtered. The reaction mixture was analysed by GC (as described below).

For reactions with $Pd(P^tBu_3)_2$ completed under conditions optimised by Dilauro *et al*., a modified version of the procedure reported in 2021 was followed.[7] A mixture of $Pd(P(^tBu)_3)_2$ (2.5 mol%, 2.5 mg) and iodoarene (0.2 mmol) in 0.8 mL of ChCl/Urea DES was vigorously stirred at 60 °C for 10 min. Benzyl zinc bromide in THF (0.6 mmol) was added rapidly rapidly spread over the mixture, then mixture was stirred at 60 °C for 20 s. The reaction mixture was then directly extracted with DCM (3 × 2 mL). The organic layer was filtered through a Celite pad, and the solvent was removed under reduced pressure.

Table S4: Final Negishi cross-coupling substrate scope

Entry	Electrophile	Catalyst	Zn Reagent (equiv.)	GC reference compound used	Ar-R^2 Conv. (%)	Ar-H Conv. (%)	Ar-I Recov. (%)	Ar-Ar Conv. (%)
1[ac]	Iodobenzene	$Pd_3(OAc)_2$	a (2)	Biphenyl	61	-	37	2
2[a]	Iodobenzene	$Pd_3(OAc)_2$	b (3)	Biphenyl	93	-	7	0
3[a]	2-(2iodophenyl)pyridine	$Pd_3(OAc)_2$	a (3)	2-(2iodophenyl)pyridine	25	13	33	12
4[a]	2-(2iodophenyl)pyridine	$Pd_3(OAc)_2$	b (3)	2-(2iodophenyl)pyridine	77	7	13	2
5[a]	N,N-Diethyliodobenzamide	$Pd_3(OAc)_2$	a (2)	Diethylbenzamide	96	0	4	0
6[b]	N,N-Diethyliodobenzamide	$Pd_3(OAc)_2$	b (2)	*o*-Toluidine ester	94	1	5	0
7[a]	Methyl-2-iodobenzoate	$Pd_3(OAc)_2$	a (2)	Methyl benzoate	97	3	0	0
8[a]	Methyl-2-iodobenzoate	$Pd_3(OAc)_2$	b (2)	*o*-Toluidine ester	84	2	14	0
9[a]	Methyl-2-iodobenzoate	$Pd(OAc)_2(PPh_3)_2$	b (2)	Methyl benzoate	61	8	30	0
10[a]	Methyl-2-iodobenzoate	$Pd(P^tBu_3)_2$	b (2)	Methyl benzoate	63	9	27	0
11[ad]	Methyl-2-iodobenzoate	$Pd(P^tBu_3)_2$	b (2)	Methyl benzoate	98	2	0	0
12[a]	Methyl-2-iodobenzoate	$Pd_3(OAc)_2$	c (2)	Methyl benzoate	36	17	28	0
13[a]	Methyl-2-iodobenzoate	$Pd_3(OAc)_2$	c (4)	Methyl benzoate	77	14	8	0
14a	Methyl-2-iodobenzoate	$Pd_3(OAc)_2$	d (2)	Methyl benzoate	52	10	38	0
15[a]	Methyl-2-iodobenzoate	$Pd_3(OAc)_2$	d (4)	Methyl benzoate	85	6	8	0
16[b]	1-Iodo-2-(methoxymethyl)benzene	$Pd_3(OAc)_2$	a (3)	Biphenyl	49	7	32	0
17[b]	1-Iodo-2-(methoxymethyl)benzene	$Pd_3(OAc)_2$	b (2)	Biphenyl	85	1	14	0
18[b]	2-Iodobenzanilide	$Pd_3(OAc)_2$	a (3)	Benzanilide	55	19	26	0
19[b]	2-Iodobenzanilide	$Pd_3(OAc)_2$	b (3)	Benzanilide	94	4	2	0
20[a]	2-Iodoacetophenone	$Pd_3(OAc)_2$	a (2)	Acetophenone	86	1	11	2
21[b]	2-Iodoacetophenone	$Pd_3(OAc)_2$	b (2)	Acetophenone	92	1	5	0
22[a]	Methyl-3-iodobenzoate	$Pd_3(OAc)_2$	b (2)	Methyl benzoate	43	4	40	0
23[a]	Methyl-3-iodobenzoate	$Pd(OAc)_2(PPh_3)_2$	b (2)	Methyl benzoate	52	4	43	0
24[a]	Methyl-3-iodobenzoate	$Pd(P^tBu_3)_2$	b (2)	Methyl benzoate	93	3	4	0
25[ad]	Methyl-3-iodobenzoate	$Pd(P^tBu_3)_2$	b (2)	Methyl benzoate	94	3	0	0
26[a]	Methyl-4-iodobenzoate	$Pd_3(OAc)_2$	b (2)	Methyl benzoate	60	2	38	0
27[b]	Methyl-4-iodobenzoate	$Pd(OAc)_2(PPh_3)_2$	a (3)	Methyl benzoate	72	6	0	14
28[b]	Methyl-4-iodobenzoate	$Pd(OAc)_2(PPh_3)_2$	b (3)	*o*-Toluidine ester	71	16	13	0
29[a]	Methyl-4-iodobenzoate	$Pd(P^tBu_3)_2$	b (2)	Methyl benzoate	82	0	6	0
30[ad]	Methyl-4-iodobenzoate	$Pd(P^tBu_3)_2$	b (2)	Methyl benzoate	75	2	11	0
31[b]	4-Iodoacetophenone	$Pd(OAc)_2(PPh_3)_2$	a (3)	Acetophenone	72	6	0	11
32[b]	4-Iodoacetophenone	$Pd(OAc)_2(PPh_3)_2$	b (3)	*o*-Toluidine ester	52	5	44	0
33[b]	4-Iodoanisole	$Pd(OAc)_2(PPh_3)_2$	a (3)	Anisole	66	13	0	7
34[b]	4-Iodoanisole	$Pd(OAc)_2(PPh_3)_2$	b (3)	*o*-Toluidine ester	33	20	47	0
35[b]	4-Iodotoluene	$Pd(OAc)_2(PPh_3)_2$	a (3)	Naphthalene	75	-	0	22
36[b]	4-Iodotoluene	$Pd(OAc)_2(PPh_3)_2$	b (3)	Biphenyl	23	-	67	0
37[a]	1-Iodonaphthalene	$Pd(OAc)_2(PPh_3)_2$	a (3)	Naphthalene	66	17	9	0
38[b]	1-Iodonaphthalene	$Pd(OAc)_2(PPh_3)_2$	b (3)	Naphthalene	46	5	27	0
40[a]	4-Bromo-1-iodobenzene	$Pd(OAc)_2(PPh_3)_2$	a (3)	Bromobenzene	95	2	1	0
41[b]	4-Bromo-1-iodobenzene	$Pd(OAc)_2(PPh_3)_2$	b (3)	Bromobenzene	53	4	43	0
42[b]	4-Iodonitrobenzene	$Pd(OAc)_2(PPh_3)_2$	a (3)	Nitrobenzene	68	5	2	25

43[b]	4-Iodonitrobenzene	$Pd(OAc)_2(PPh_3)_2$	b (3)	*o*-Toluidine ester	11	40	9	0
44[b]	Methyl 2-bromobenzoate	$Pd(OAc)_2(PPh_3)_2$	a (2)	Methyl benzoate	44	3	53	0

GC conversions for the substrate scopes with *ortho*- and *para* or *meta*- substituted iodarenes. [a] GC column DB-5 [b] GC column Rxi-17. [c] $Pd_3(OAc)_6$ (2 mol % Pd). [d] conditions from Dilauro *et al*.

Competition experiments

A round-bottom flask was loaded with $Pd_3(OAc)_6$ (4.5 mg, 2 mol % Pd) with ChCl/U DES (5 mL) and stirred at 60 °C to solubilise (around 10 minutes). Methyl 2-iodobenzoate (130 mg, 0.5 mmol, 1 equiv) added and mixture stirred at 60 °C for a further 10 minutes. Cyclohexyl zinc bromide or 3-cyanopropyl zinc bromide (2 mL, 1 mmol, 2 equiv) added to Schlenk under N_2 containing ^{n}BuZnCl (1 mmol, 2 equiv). Alkylzinc mixture added dropwise to DES mixture, then mixture stirred at 60 °C for 5 minutes before being quenched with NH_4Cl (2M, 15 mL). The product was extracted with DCM (3 x 15 mL), washed with deionised water (30 mL) and brine (30 mL), dried over $MgSO_4$ then filtered and concentrated *in vacuo.* Reaction mixture analysed by ^1H NMR.

Table S5: Competition experiments

Entry	Zinc Reagent	**2a/2d** or **2e** Conv. (%)	**2a** Conv. (%)	**3** Conv. (%)	**Ar-I** Recov. (%)
1	Cyclohexyl zinc bromide	32	36	11	21
2	3-cyanopropylzinc bromide	6	23	5	66

Reactivity of palladacycles

2-phenylpyridine palladacycle (**18**): Synthesis from literature procedure.[8] 2-phenylpyridine (104 mg, 1.32 mmol, 1 equiv), $Pd_3(OAc)_6$ (300 mg, 0.66 mmol, 1 equiv) and CH_2Cl_2 (20 mL) added to round-bottom flask and mixture stirred at room temperature for 3 hours. Solvent was then removed under reduced pressure and remaining solid washed with diethyl ether and filtered. Yellow powder obtained, 65% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (br s, 1H, (2)), 7.38 (t, *J* = 7.8 Hz, 1H (3)), 7.10 (d, *J* = 8.13 Hz, 1H, (5)), 6.93 (m, 1H, (4)), 6.84 (m, 3H, (6)), 6.47 (t, *J* = 5.80 Hz, 1H, (7)), 2.29 (s, 3H (1)).

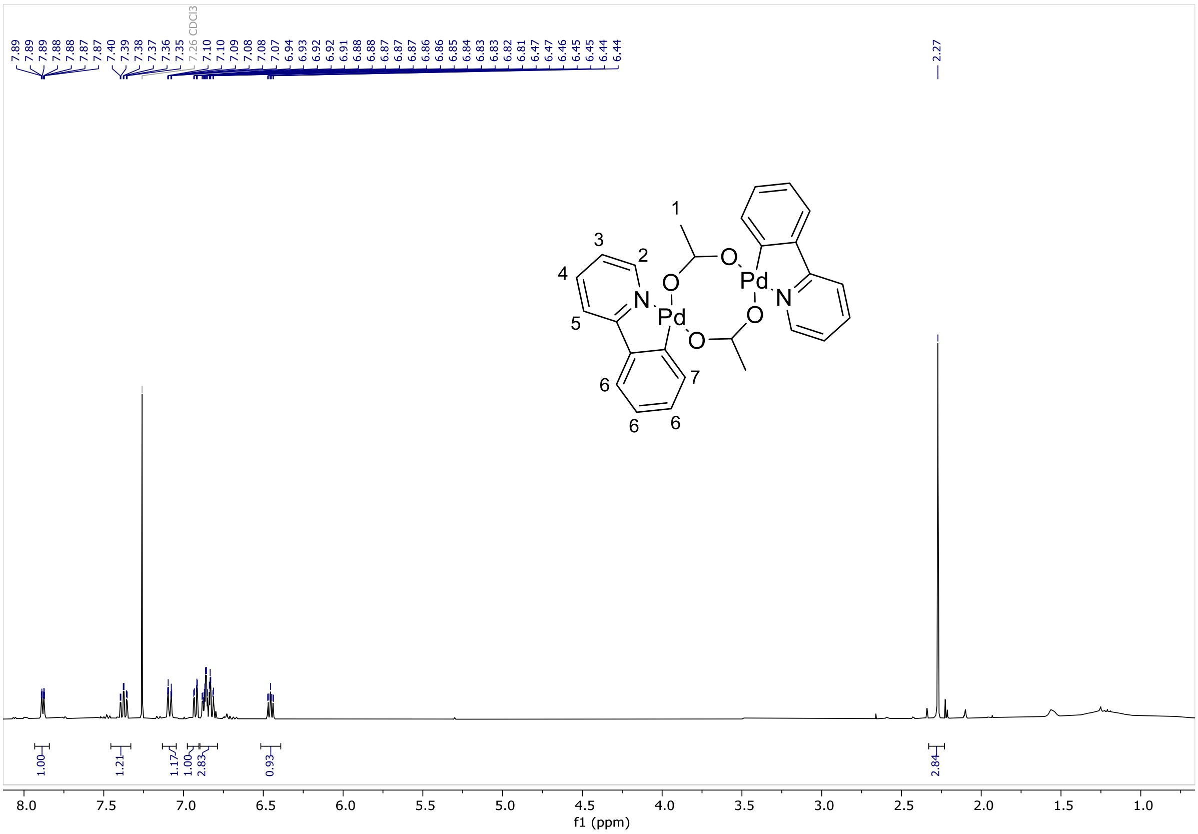


Figure S7: ^{1}H NMR spectrum of 2-phenylpyridine palladacycle

For the stoichiometric reaction, 2-phenylpyridine palladacycle (33 mg, 0.05 mmol, 0.1 equiv) added to 10 mL of ChCl/Urea DES. The mixture was heated to 60 °C and stirred for 10 mins to homogenise. Then, a solution of benzyl zinc bromide in dry THF 0.1 M (2 mmol, 2 equivalents/Pd) was added in a dropwise fashion (1 drop every 3 seconds approximately) while stirring vigorously. The reaction mixture was stirred at 60 °C for 5 minutes, then quenched with 15 mL of a 2M solution of ammonium chloride, extracted with CH_2Cl_2 (3 x 15 mL), washed with 30 mL of deionized water and 30 mL of brine, dried over $MgSO_4$ and filtered. The reaction mixture was analysed by GC.

For the catalytic reaction, 2-phenylpyridine palladacycle (8.1 mg, 5 mol% Pd) and 2-methyliodobenzoate (130 mg, 0.5 mmol, 1 equiv) added to 5 mL of ChCl/Urea DES. The mixture was heated to 60 °C and stirred for 10 mins to homogenise. Then, a solution of benzyl zinc bromide in dry THF (1.5 mmol, 3 equiv.) was added in a dropwise fashion (1 drop every 3 seconds approximately) while stirring vigorously. The reaction mixture was stirred at 60 °C for 5 minutes, then quenched with 15 mL of a saturated solution of ammonium chloride, extracted with CH_2Cl_2 (3 x 15 mL), washed with 30 mL of deionized water and 30 mL of brine, dried over $MgSO_4$ and filtered. The reaction mixture was analysed by ^1H NMR, with a calculated 89% conversion of aryl iodide to cross-coupled product.

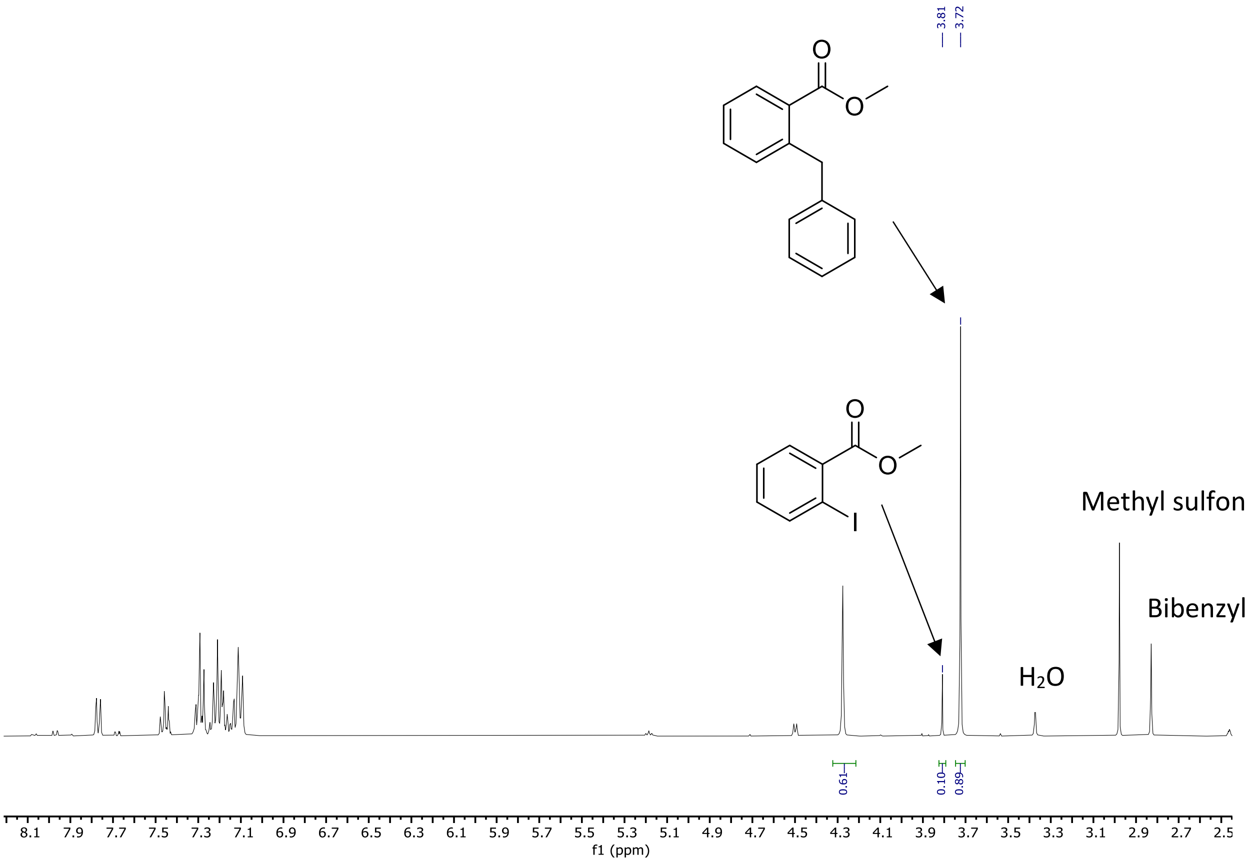


Figure S8: ^1H NMR of reaction between methyl 2-iodobenzoate and benzylzinc bromide, with 2-phenylpyridine palladacycle as catalyst. Methyl sulfone added as internal standard but was not used to calculate conversion due to solubility concerns.

Preparation of Polyiodated Substrates

<u>Methyl 2,5-diiodobenzoate</u>: 2,5-diodobenzoic acid (1.7g, 4 mmol) was placed in a round-bottom flask equipped with a magnetic stirrer bar. The acid was dissolved in 30 mL of methanol and 0.05 mL of concentrated sulfuric acid (20 mol%) was added. A condenser was equipped and the reaction refluxed for 72h. After this, the solvent was removed under vacuum and the crude dissolved in 30 mL of dichloromethane. The organic solution was washed with saturated $NaHCO_3$ aqueous solution 5 x 30 mL, dried over $MgSO_4$ and analyzed by NMR. Brown powder was obtained, yield 79%.

^1H NMR ($(CD_3)_2CO$, 500 MHz): δ 8.07 (d, *J* = 2.2 Hz, 1H, (1)), 7.80 (d, *J* = 8.3 Hz, 1H, (3)), 7.62 (dd, *J* = 8.3, 2.2 Hz, 1H, (2)), 3.91 (s, 3H, (4)).

Figure S9: ^{1}H NMR spectrum of methyl 2,5-diiodobenoate

Methyl 2,3,5-triiodobenzoate: 2,3,5-triiodobenzoic acid (5g, 0.01 mol) was placed in a round-bottom flask equipped with a magnetic stirrer bar. The acid was dissolved in 60 mL of methanol and 0.11 mL of concentrated sulfuric acid (20 mol%) was added. A condenser was equipped and the reaction refluxed for 6h. After this, the solvent was removed under vacuum and the crude dissolved in 30 mL of dichloromethane. The organic solution was washed with saturated $NaHCO_3$ aqueous solution 5 x 30 mL, dried over $MgSO_4$ and analyzed by NMR. An orange powder was obtained, yield 68%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (s, 1H, (2)), 7.75 (s, 1H, (1)), 3.93 (s, 1H, (3)).

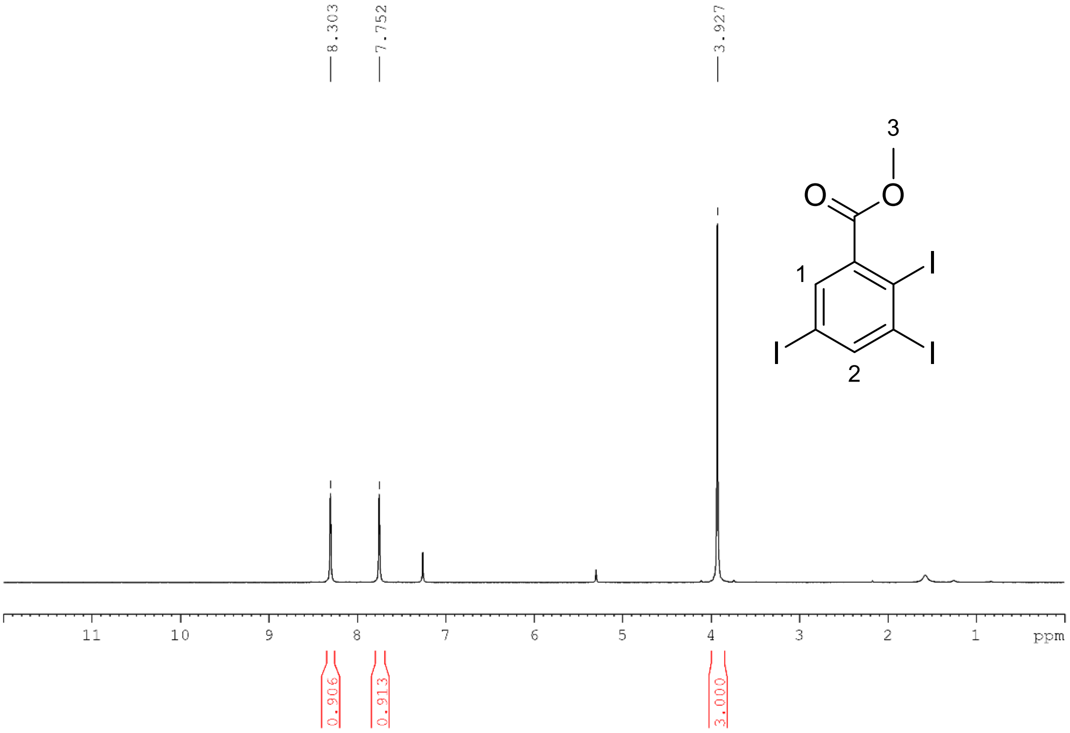


Figure S10: ^{1}H NMR spectrum of Methyl 2,3,5-triiodobenzoate

Procedure for the Negishi coupling between polysubstituted iodoarene and benzyl zinc (manuscript scheme 6 and scheme 7)

A round-bottom flask was loaded with $Pd_3(OAc)_6$ (5 mol % Pd), $Pd(OAc)_2(PPh_3)_2$ (5 mol%) or $Pd(P^tBu_3)_2$ (5 mol%), polysubstituted iodoarene (1 equiv.) and 5 mL of ChCl/Urea DES. The mixture was heated to 60 ^{o}C and stirred at 1000 rpm until the reaction became orange (around 10 minutes). Then, a solution of benzyl zinc bromide in dry THF (2 equivalents) was added in a dropwise fashion (1 drop every 3 seconds approximately) while stirring vigorously. The reaction mixture was stirred at 60 ^{o}C for 5 minutes, then quenched with 15 mL of a 2M solution of ammonium chloride, extracted with CH_2Cl_2 (3 x 15 mL), washed with 30 mL of deionized water and 30 mL of brine, dried over $MgSO_4$ and filtered. The reaction mixture was analysed by GC (as described below).

For reactions with $Pd(P^tBu_3)_2$ completed under conditions optimised by Dilauro *et al.*, reactions were completed as with the monosubstituted iodoarenes. A mixture of $Pd(P(^tBu)_3)_2$ (2.5 mol%, 2.5 mg) and iodoarene (0.2 mmol) in 1 mL of ChCl/Urea DES was vigorously stirred at 60 °C for 10 min. Benzyl zinc bromide in THF (0.6 mmol) was added rapidly rapidly spread over the mixture, then mixture was stirred at 60 °C for 20 s. The reaction mixture was then directly extracted with DCM (3

× 2 mL). The organic layer was filtered through a Celite pad, and the solvent was removed under reduced pressure.[7] The reaction mixture was analysed by GC (as described below).

Characterisation of for the Negishi coupling between 2,3,5-triiodobenzoate and benzyl zinc

For purification of the *ortho*-substituted product in the reaction between 2,3,5-triiodobenzoate and benzyl zinc bromide in the presence of $Pd_3(OAc)_6$. The GC internal standard was removed from the crude by flash column chromatography on silica gel 220-440 mesh using Hexane/Ethyl Acetate 99:1 as eluent. The product was then further purified using a CombiFlash Rf system equipped with a RediSep Rf silica column for 20 mg to 0.4 g sample, using a flow rate of 18 mL/min and a gradient of dichloromethane in hexane from 0% to 5% over 20 minutes. The purified sample was analysed by ^1H and ^{13}C NMR spectroscopy.

^1H NMR ($CDCl_3$, 600 MHz): δ 8.37 (d, *J* = 1.9 Hz, 1H, (4)), 8.10 (d, *J* = 1.9 Hz, 1H, (2)), 7.24 (tt, *J* = 7.7, 1.7 Hz, 2H, (12, 14)), 7.17 (tt, *J* = 7.4, 1.8 Hz, 1H (10)), 7.02 (tt, *J* = 7.2, 1.1 Hz, 2H, (11, 15)), 4.52 (s, 2H, (9)), 3.76 (s, 1H, (8)).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ 166.1 (7), 150.5 (4), 142.9 (6), 138.9 (2), 138.6 (10), 134.0 (1), 128.5 (11, 15), 128.3 (12, 14), 125.9 (13), 105.5 (5), 91.9 (3), 52.3 (9), 42.3 (8).

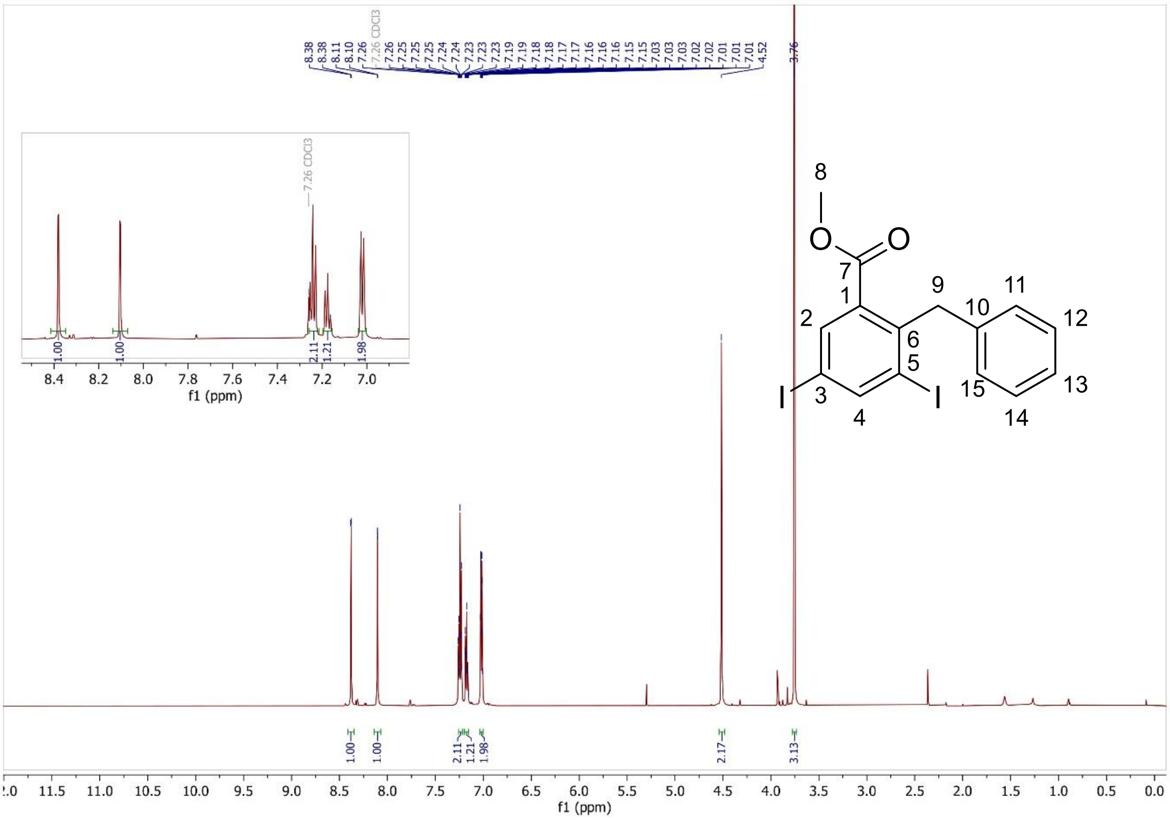


Figure S11: ^1H NMR spectrum of major product (**23i**) from Negishi coupling between methyl 2,3,5 triiodobenzoate and benzyl zinc catalysed by Pd acetate in DES.

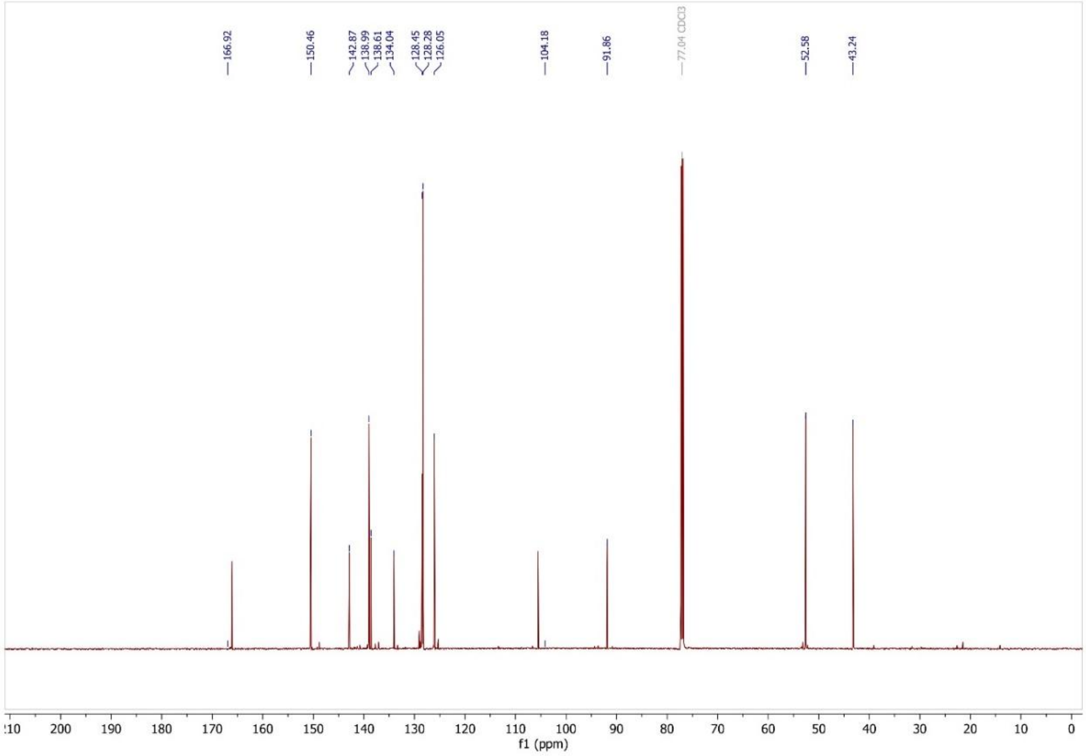


Figure S12: ^{13}C NMR spectrum of major product (**23i**) from Negishi coupling between methyl 2,3,5 triiodobenzoate and benzyl zinc catalysed by Pd acetate in DES.

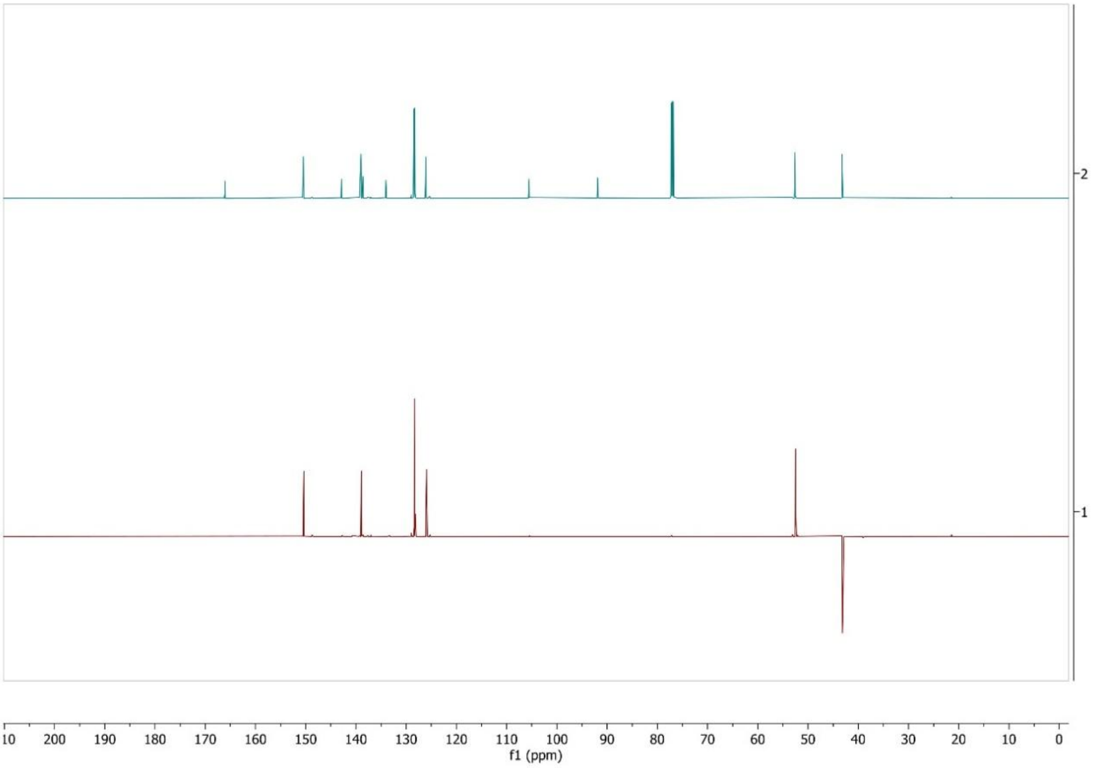


Figure S13: DEPT-135 experiment contrasted against ^{13}C spectrum of major product (**23i**) from Negishi coupling between methyl 2,3,5 triiodobenzoate and benzyl zinc catalysed by Pd acetate in DES.

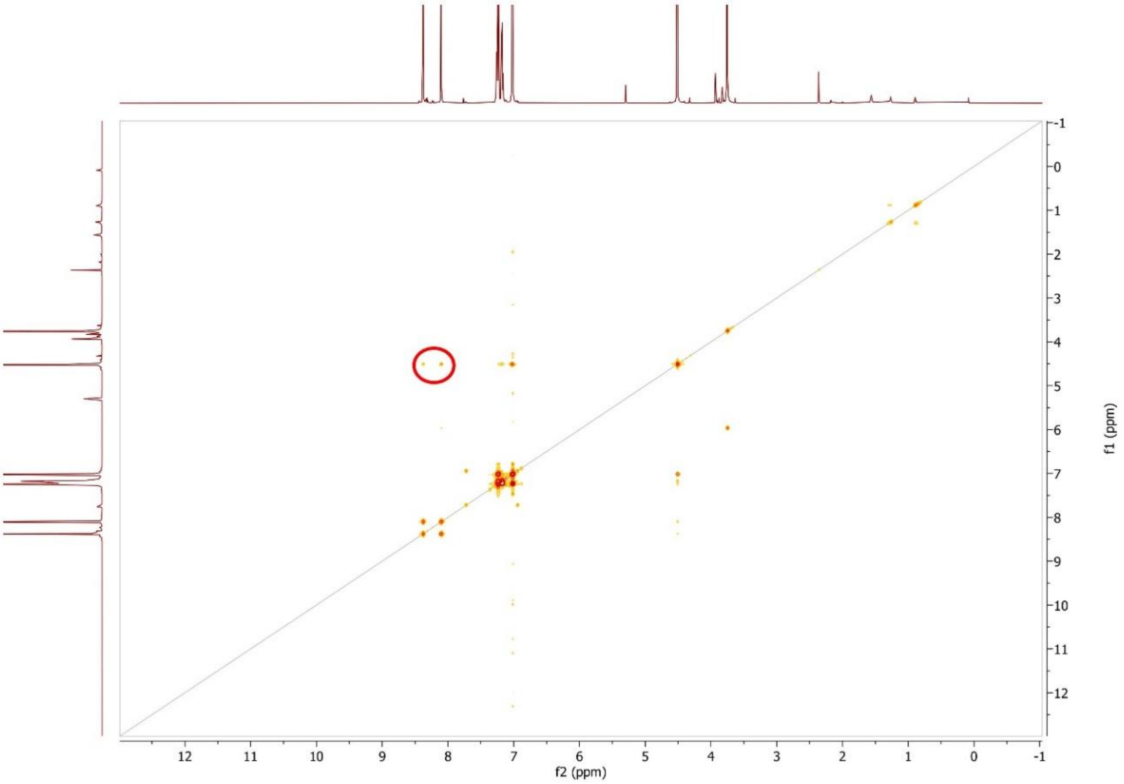


Figure S14: ^1H-^1H COSY NMR spectrum of major product (**23i**) from Negishi coupling between methyl 2,3,5 triiodobenzoate and benzyl zinc catalysed by Pd acetate in DES.

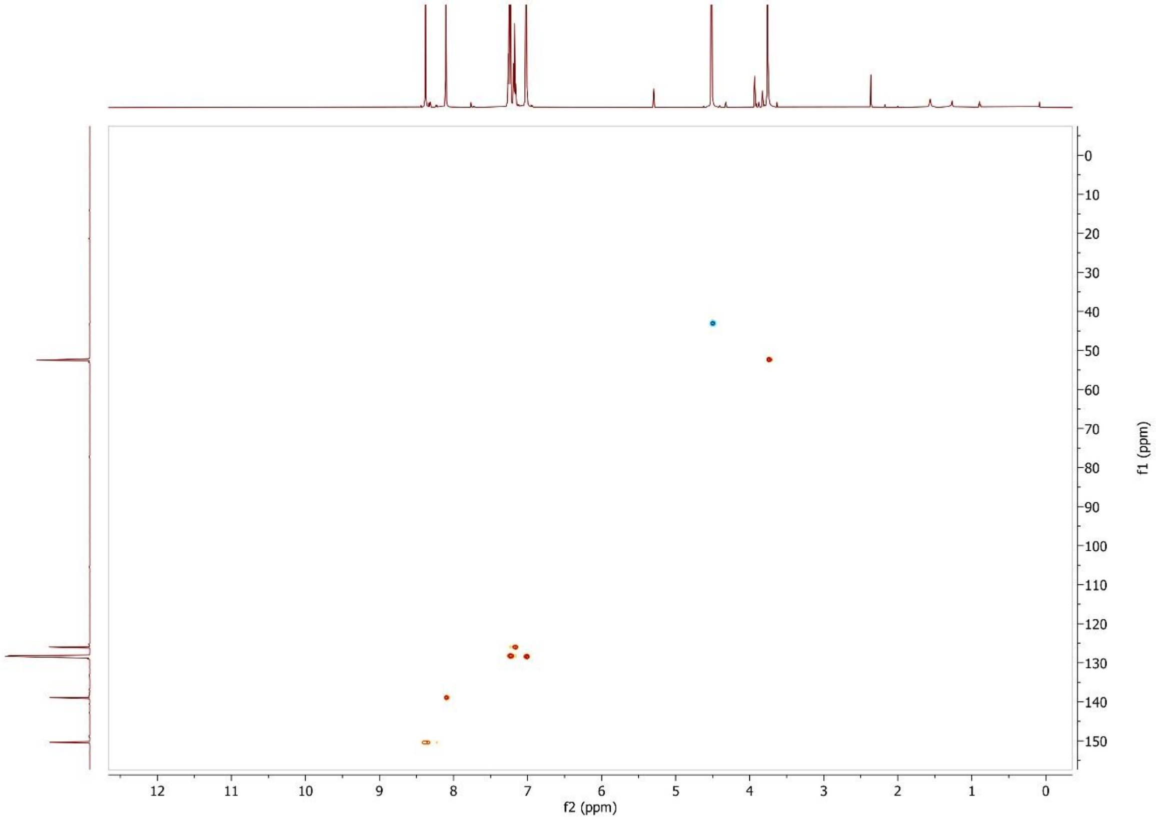


Figure S15: ^{1}H-^{13}C HSQC NMR spectrum of major product (**23i**) from Negishi coupling between methyl 2,3,5 triiodobenzoate and benzyl zinc catalysed by Pd acetate in DES.

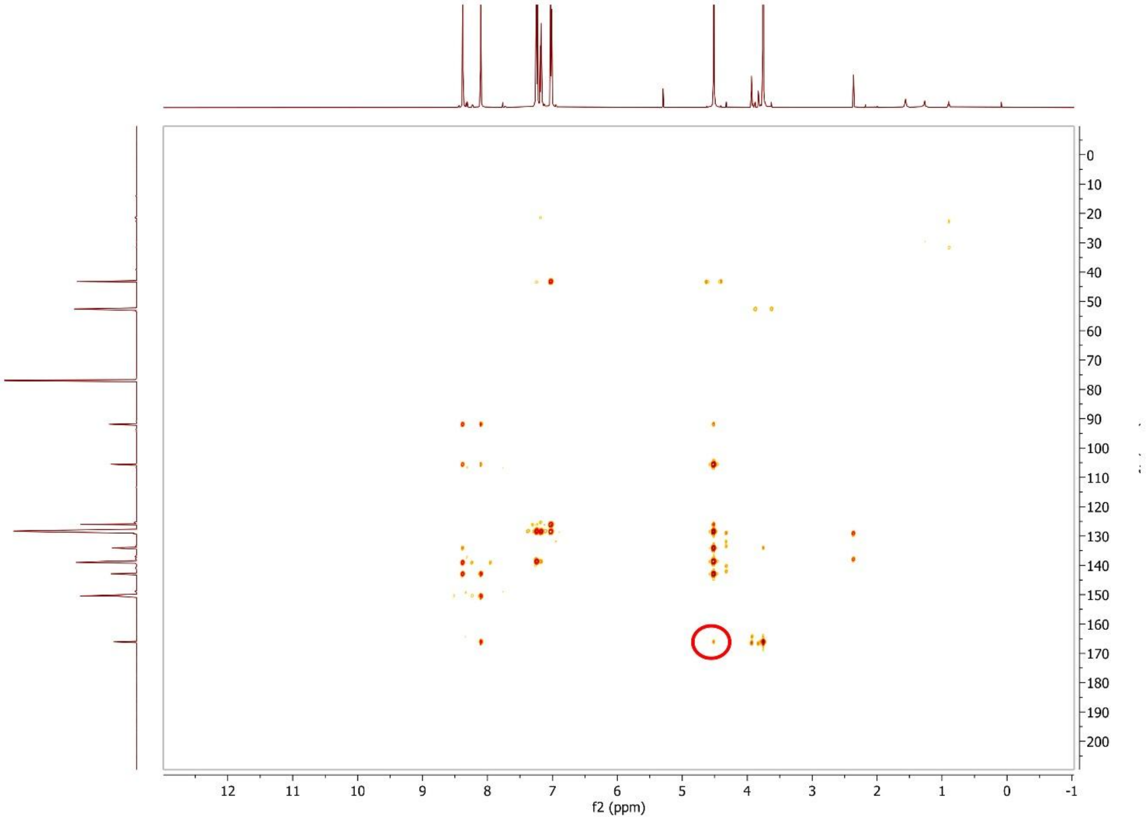


Figure S16: ^{1}H-^{13}C HMBC NMR spectrum of major product (**23i**) from Negishi coupling between methyl 2,3,5 triiodobenzoate and benzyl zinc catalysed by Pd acetate in DES.

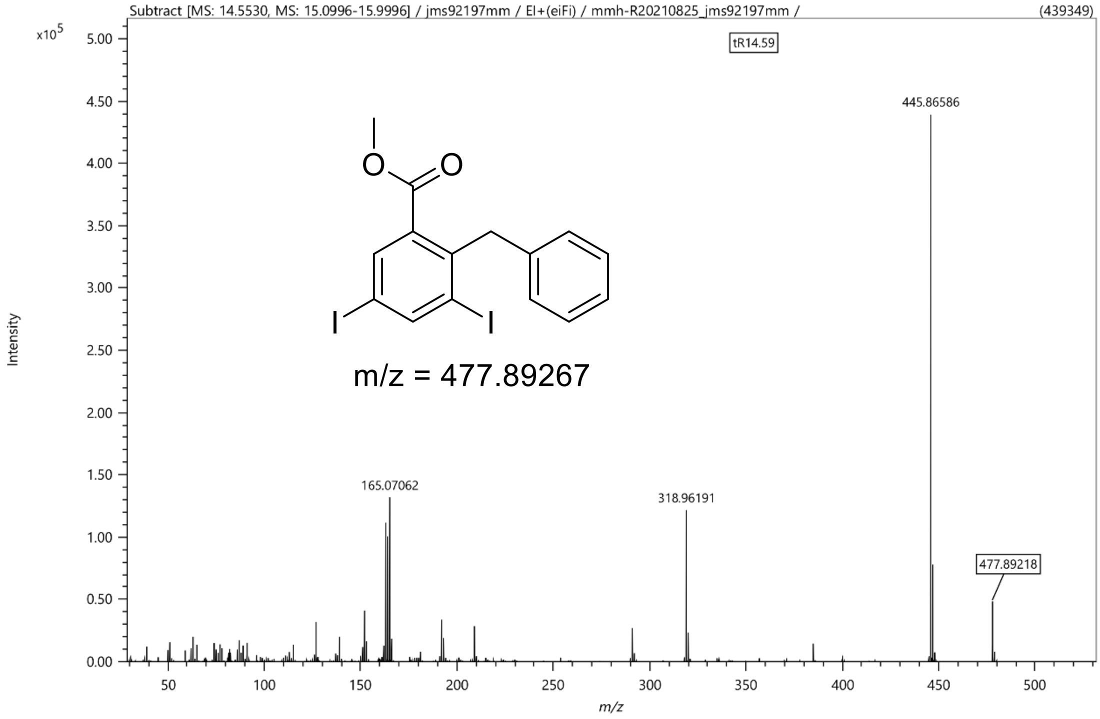
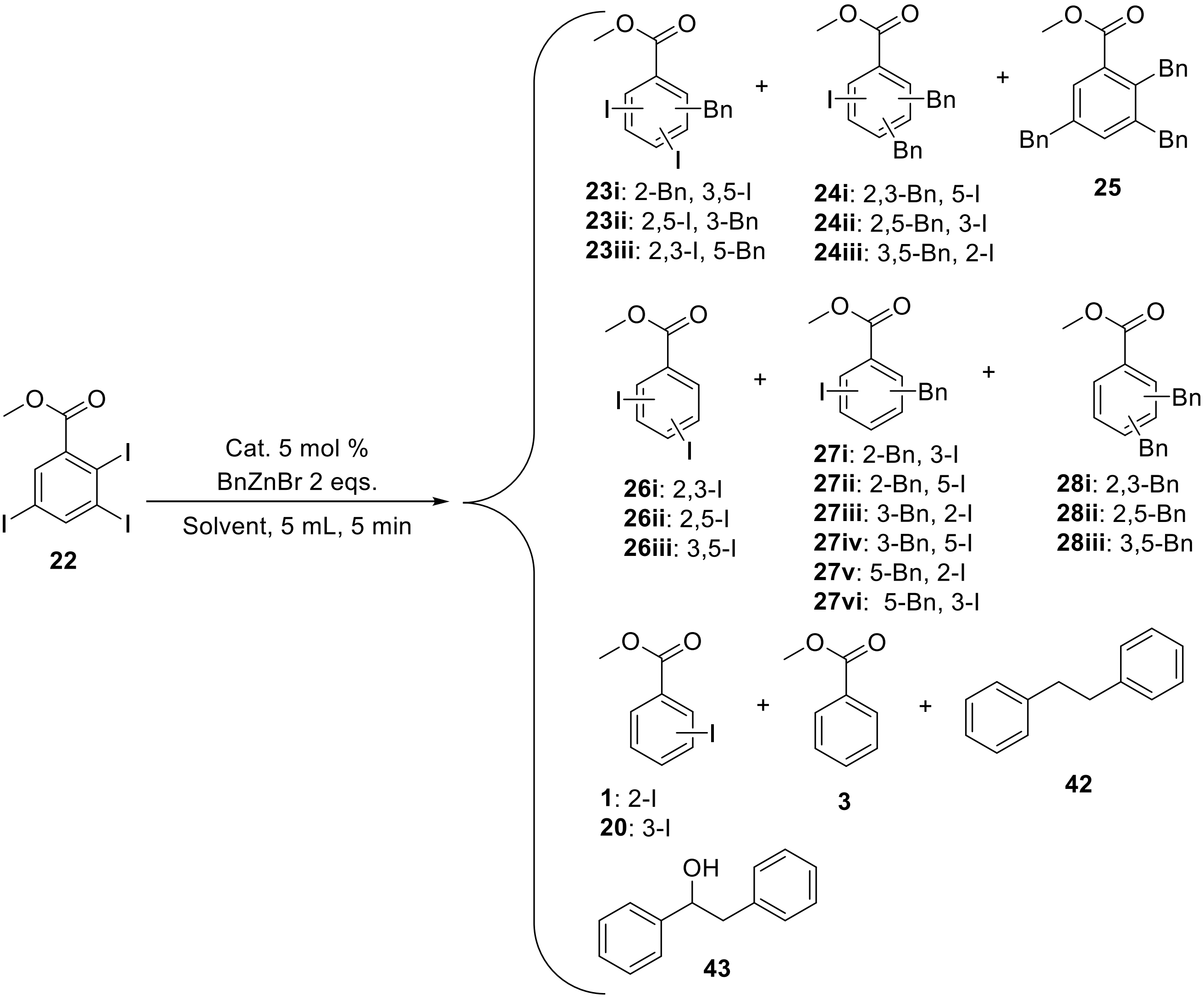


Figure S17: Electron-ionisation mass spectrum for **23i**.



Scheme S4: Detected compounds in the reaction mixtures from the Negishi coupling between methyl 2,3,5-triiodobenzoate and benzyl zinc bromide.

Table S6: Conversions for the coupling between methyl 2,3,5-triiodobenzoate and benzyl zinc bromide in the presence of $Pd_3(OAc)_6$

Entry	Electrophile	GC reference compound used	Conversion in DES (%)	Conversion in THF (%)
1[a]	**22**	22	12	0
2[a]	**23i**	Methyl 2-iodobenzoate	70	10
3[a]	**23ii-iii**	Methyl 2-iodobenzoate	2	28
4[a]	**24i-iii**	Methyl 2-iodobenzoate	4	35
5[a]	**25**	Methyl 2-iodobenzoate	5	15
6[a]	**27i-vi**	Methyl 2-iodobenzoate	4	11
7[a]	**28i-iii**	Methyl 2-iodobenzoate	2	2
8[a]	**26i-iii**	Methyl 2-iodobenzoate	1	0
9[a]	**1, 20**	Methyl 2-iodobenzoate	0	0
10[a]	**4**	Methyl benzoate	-	trace

[a]Reaction analysed by GC with a Rxi-17 column. DES conditions: ChCl/urea, 60 °C, 5 min. THF conditions: $[NBu_4]Br$ 0.2 M, 40 °C, 5 min.

Characterisation of for the Negishi coupling between polyidodoarenes and benzyl zinc

Table S7: Conversions for the coupling between methyl 2,3,5 triiodobenzoate and benzyl zinc bromide in the presence of $Pd(OAc)_2(PPh_3)_2$

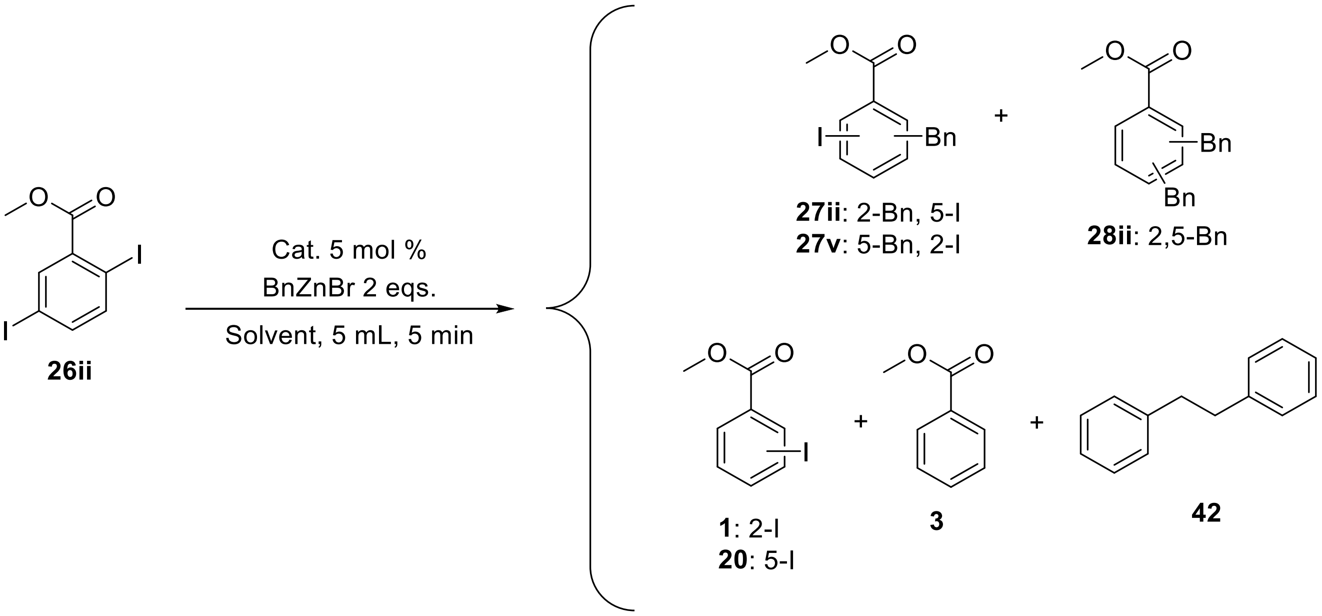
Entry	Electrophile	GC reference compound used	Conversion in DES (%)
1	**22**	22	40
2	**23i**	Methyl 2,5-benzoate	45
3	**25**	Methyl benzoate	3
4	**26i-iii**	Methyl 2,5-diiodobenzoate	5
5	**1, 20**	Methyl 4-iodobenzoate	7

Table S8: Conversions for the coupling between methyl 2,3,5-triiodobenzoate and benzyl zinc bromide in the presence of $Pd(P^tBu_3)_2$

Entry	Electrophile	GC reference compound used	Conversion in DES (%)
1	**22**	22	38
2	**23i**	Methyl 2,5-diiodobenzoate	20
3	**23ii-iii**	Methyl 2,5-diiodobenzoate	4
4	**25**	Methyl benzoate	13
5	**26i-iii**	Methyl 2,5-diiodobenzoate	5
6	**1, 20**	Methyl 4-iodobenzoate	7

Table S9: Conversions for the coupling between methyl 2,3,5-triiodobenzoate and benzyl zinc bromide in the presence of $Pd(P^tBu_3)_2$ under conditions optimised by Dilauro *et al*.[7]

Entry	Electrophile	GC reference compound used	Conversion in DES (%)
1	**22**	22	16
2	**23i**	Methyl 2,5-diiodobenzoate	45
3	**23ii-iii**	Methyl 2,5-diiodobenzoate	2
5	**25**	Methyl benzoate	7
7	**24i-iii**	Methyl 4-iodobenzoate	11
9	**1, 20**	Methyl 4-iodobenzoate	3



Scheme S5: Detected compounds in the reaction mixtures from the Negishi coupling between methyl 2,5-diiodobenzoate and benzyl zinc bromide.

Table S10: Conversions for the coupling between methyl 2,5 diiodobenzoate and benzyl zinc bromide in the presence of $Pd_3(OAc)_6$

Entry	Electrophile	GC reference compound used	Conversion in DES (%)
1	**26ii**	26ii	17
2	**27ii**	Methyl 4-iodobenzoate	64
3	**27v**	Methyl 4-iodobenzoate	0
4	**28ii**	Methyl benzoate	16
5	**1, 20**	Methyl 4-iodobenzoate	4
6	**4**	Methyl benzoate	0

Table S11: Conversions for the coupling between methyl 2,5 diiodobenzoate and benzyl zinc bromide in the presence of $Pd(OAc)_2(PPh_3)_2$

Entry	Electrophile	GC reference compound used	Conversion in DES (%)
1	**26ii**	26ii	57
2	**27ii**	Methyl 4-iodobenzoate	20
3	**27v**	Methyl 4-iodobenzoate	5
4	**28ii**	Methyl benzoate	4
5	**1, 20**	Methyl 4-iodobenzoate	6
6	**4**	Methyl benzoate	6

Table S12: Conversions for the coupling between methyl 2,5 diiodobenzoate and benzyl zinc bromide in the presence of $Pd(P^tBu_3)_2$

Entry	Electrophile	GC reference compound used	Conversion in DES (%)
1	**26ii**	26ii	28
2	**27ii**	Methyl 4-iodobenzoate	16
3	**27v**	Methyl 4-iodobenzoate	0
4	**28ii**	Methyl benzoate	47
5	**1, 20**	Methyl 4-iodobenzoate	9
6	**4**	Methyl benzoate	0

Table S13: Conversions for the coupling between methyl 2,5 diiodobenzoate and benzyl zinc bromide in the presence of $Pd(P^tBu_3)_2$ under conditions optimised by Dilauro *et al*.[7]

Entry	Electrophile	GC reference compound used	Conversion in DES (%)
1	**26ii**	26ii	16
2	**27ii**	Methyl 4-iodobenzoate	25
3	**27v**	Methyl 4-iodobenzoate	0
4	**28ii**	Methyl benzoate	44
5	**1, 20**	Methyl 4-iodobenzoate	6
6	**4**	Methyl benzoate	0

GC methodology

The conversions obtained by GC were calculated by considering the integration of the product peaks according to *equations 1-3*, where RF_A is the response factor of the analyte, RRF_A is the relative response factor of the analyte and STD is an internal standard.

When the chemical response of the internal standard at the FID does not completely reproduce the chemical response of the analytes (starting materials, product, and side-products), a mass balance for the reaction that differs from 100% can be obtained. For the experiments in which a mass balance > 100% was obtained, the masses of the analytes detected in the chromatogram were normalised so that the total mass balance for all products was 100%. For cases in which mass balance < 100%, the data could not be normalised, since it is not possible to determine whether the result was due to the response of the analytes and the standard at the FID or due to mass loses during the reaction, e.g. during workup.

$$\mathrm{RF_A} = \frac{\mathrm{GC\ Peak_A}}{[\mathrm{A}]_{known}} \qquad \mathbf{1}$$

$$\mathrm{RRF_A} = \frac{\mathrm{RF_A}}{\mathrm{RF_{STD}}} \qquad \mathbf{2}$$

$$[\mathrm{A}] = \frac{\mathrm{GC\ peak_A}}{\mathrm{GC\ peak_{STD}}} \frac{[\mathrm{STD}]}{\mathrm{RRF_A}} \qquad \mathbf{3}$$

The response factors of the cross-coupled products were assumed to be equal to the response factor measured for a known reference sample of similar chemical structure. The response factors of the dehalogenated side products were assumed equal to that measured for a known reference of similar structure. The response factor of the homocoupling product of benzyl zinc bromide was assumed to be equal to that measured for biphenyl. The response factor of the homocoupling of the starting material was assumed equal to the response factor of biphenyl. Tables S3-13 list the reference compounds used for each analyte. Naphthalene or *n*-decane were used as internal standards, as indicated in the results in Tables S3-13.

Initial optimisation reactions – gas chromatograms

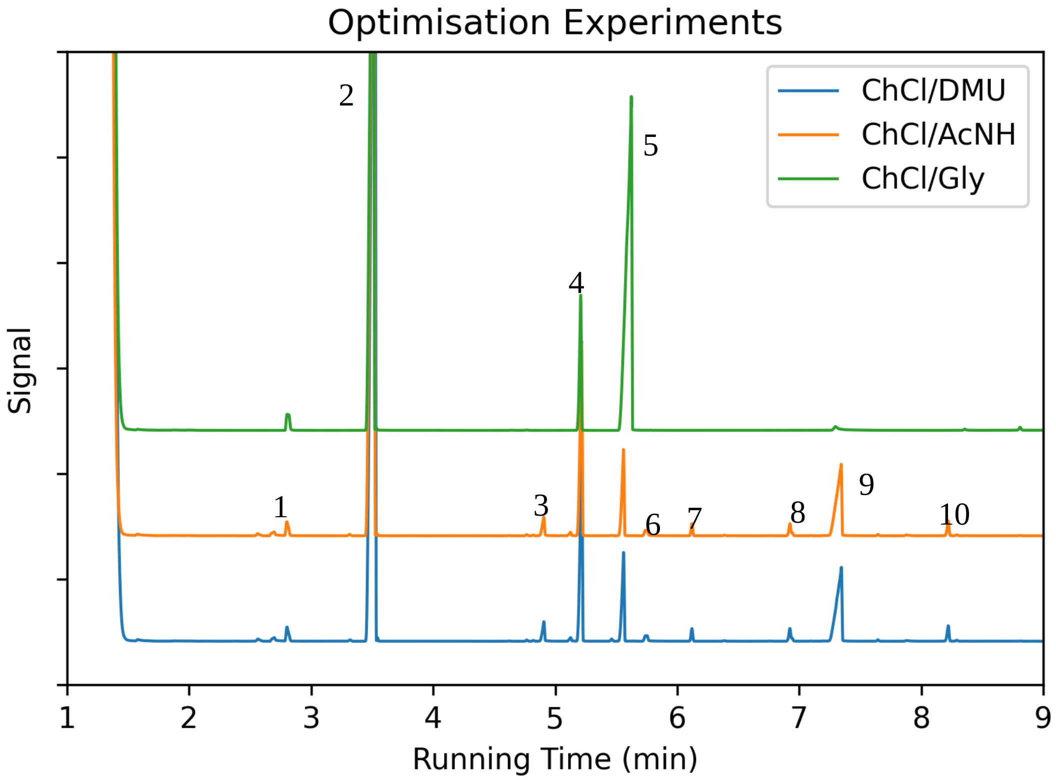
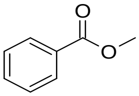
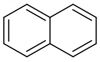
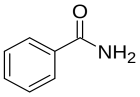
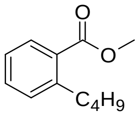
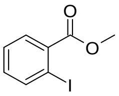
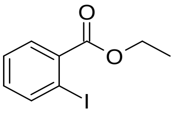
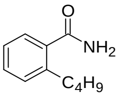
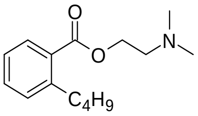
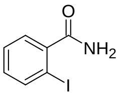
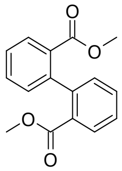
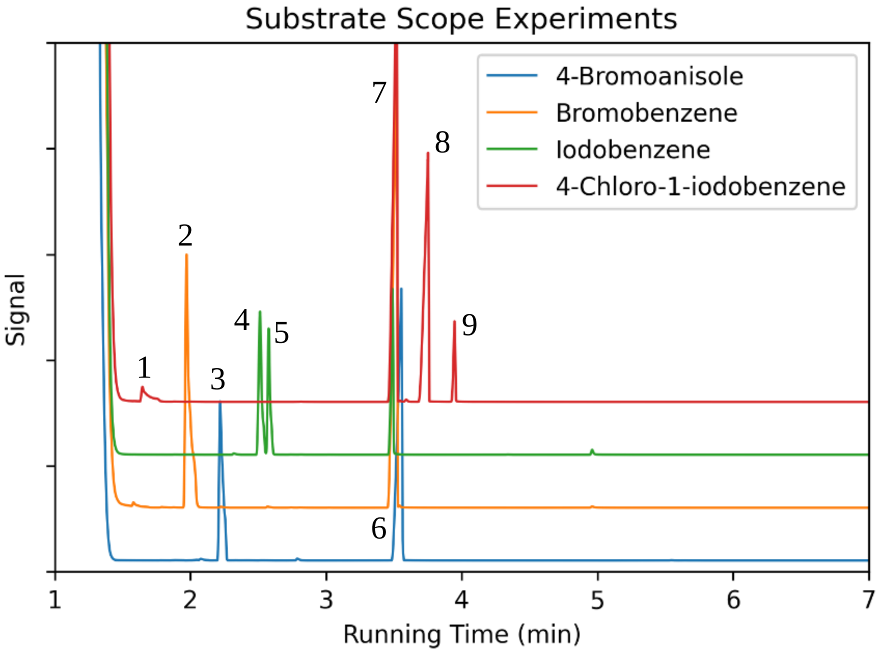


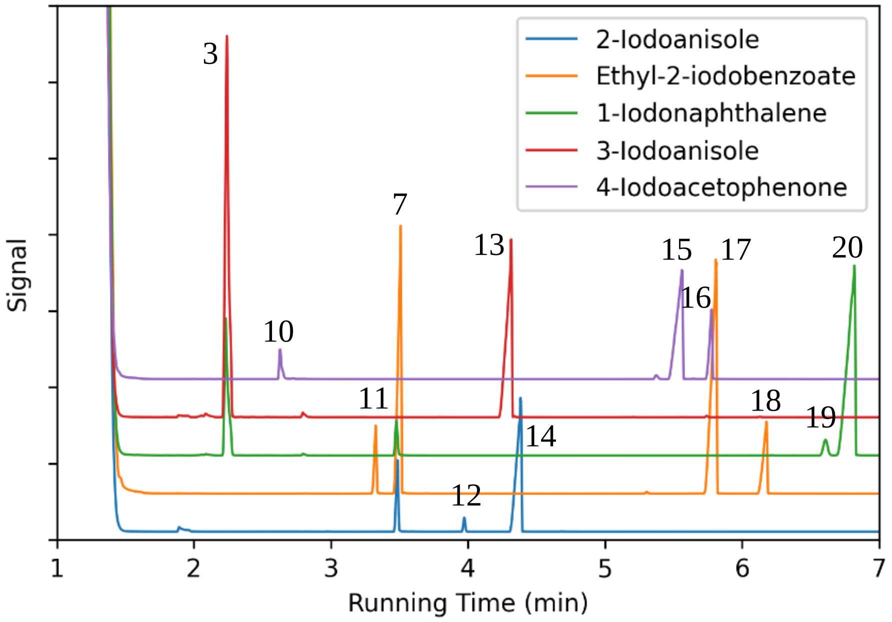
Figure S18: Gas chromatograms from the Negishi coupling between methyl 2-iodobenzoate and n-butylzinc chloride in ChCl/DMU, ChCl/AcNH and ChCl/Gly DESs. All experiments were run using the DB5 column. The structure of the compounds associated with the peaks is outlined in Table S14.

Table S14: Chemical structure of the compounds associated to the chromatograms plotted in Figure S18.

GC Peak	Formula	Structure
1	$C_8H_8O_2$	
2	$C_{10}H_8$	
3	C_7H_7NO	
4	$C_{12}H_{16}O_2$	
5	$C_8H_7IO_2$	
6	$C_9H_9IO_2$	
7	$C_{11}H_{15}NO$	
8	$C_{15}H_{23}NO_2$	
9	C_7H_6INO	
10	$C_{16}H_{14}O_4$	

Initial substrate scope – gas chromatograms





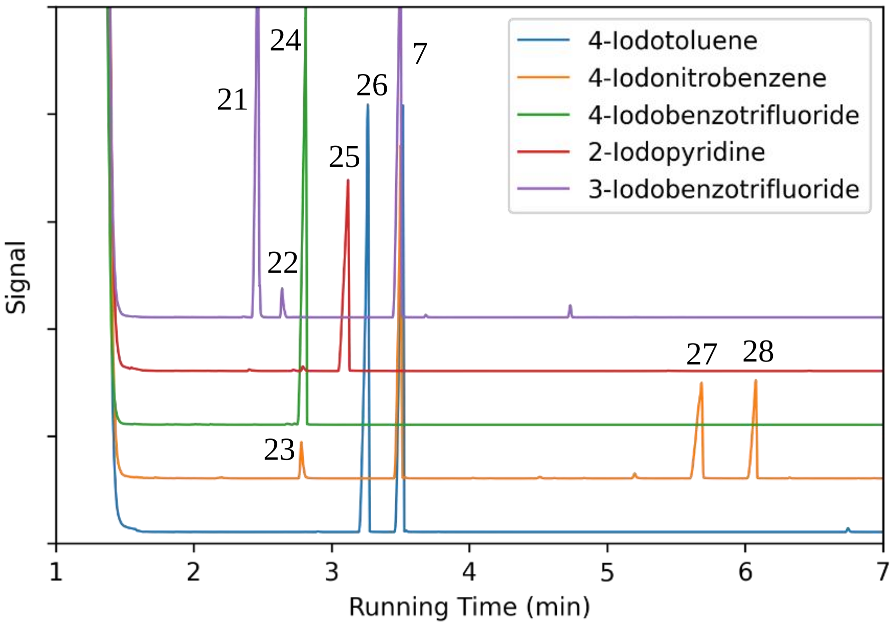
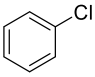
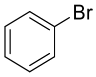
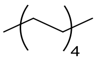
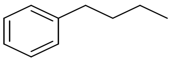
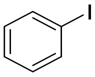
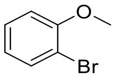
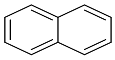
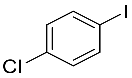
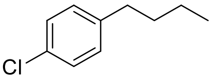
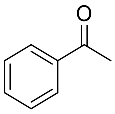
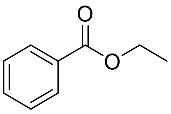
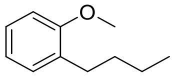
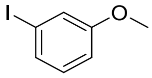
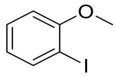
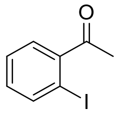
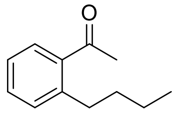
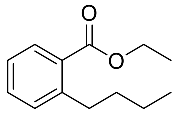
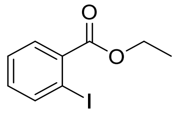
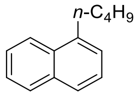
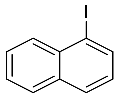
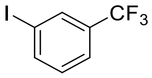
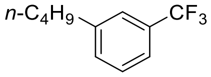
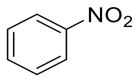
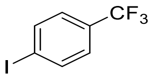
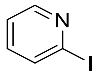
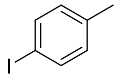
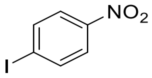
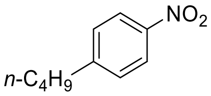


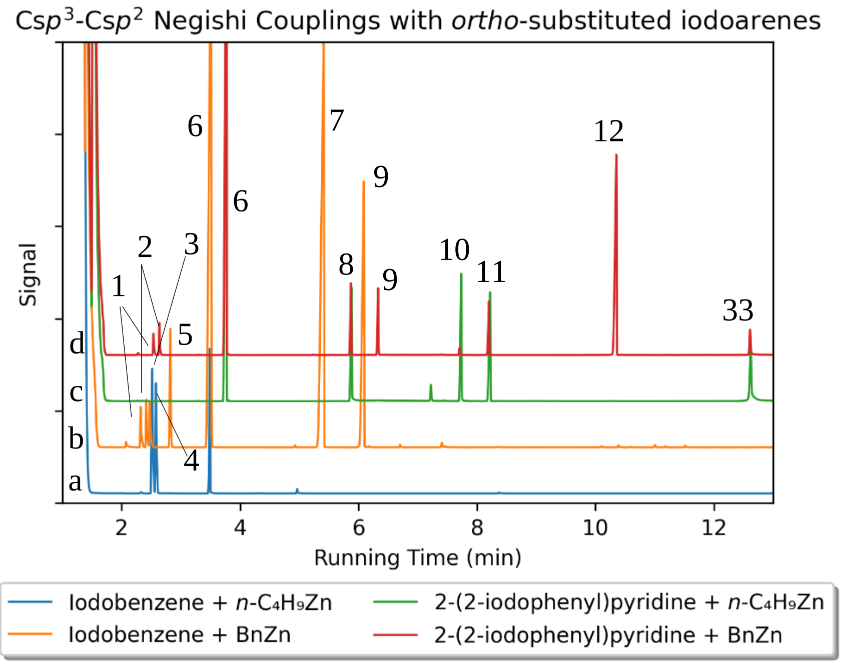
Figure S19: Initial substrate scope. Gas chromatograms from each reaction. All experiments were run in the DB5 column. The structure of the compounds associated to the peaks is outlined in Table S15.

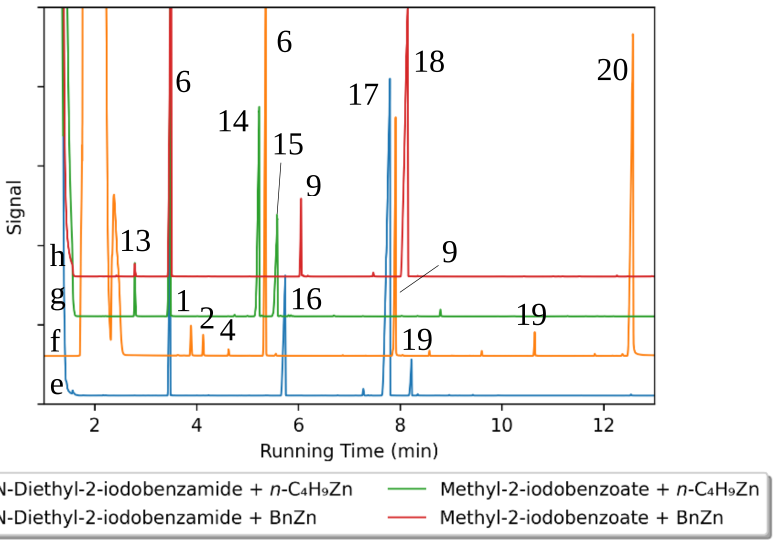
Table S15: Chemical structure of the compounds associated to the chromatograms plotted in Figure S19.

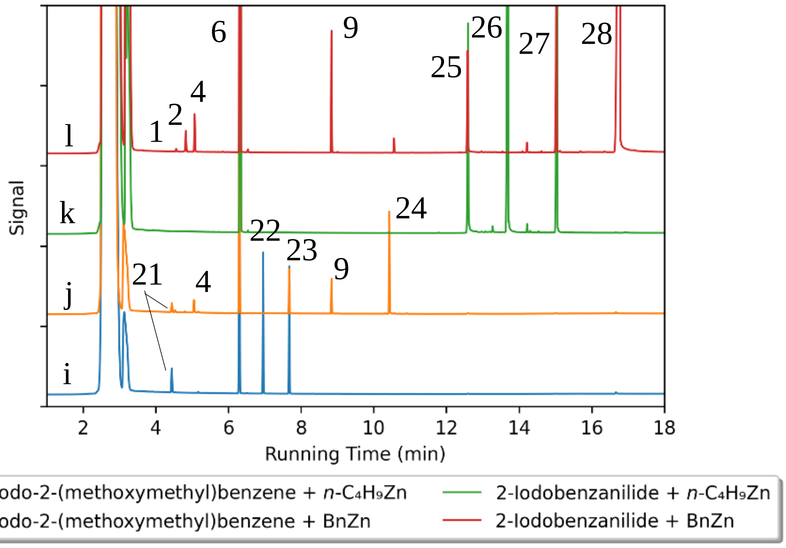
GC Peak	Formula	Structure
1	C_6H_5Cl	
2	C_6H_5Br	
3	$C_{10}H_{22}$	
4	$C_{10}H_{14}$	
5	C_6H_5I	
6	C_7H_7BrO	
7	$C_{10}H_8$	
8	C_6H_4ICl	
9	$C_{10}H_{13}Cl$	
10	C_8H_8O	
11	$C_9H_{10}O_2$	

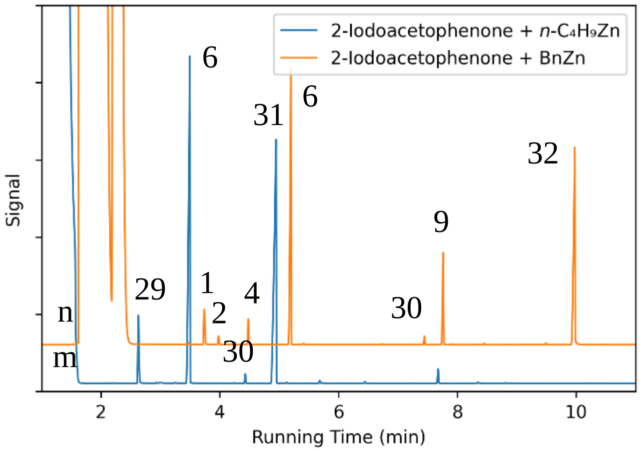
12	$C_{11}H_{16}O$	
13	C_7H_7IO	
14	C_7H_7IO	
15	C_8H_7IO	
16	$C_8H_{16}O$	
17	$C_{13}H_{18}O_2$	
18	$C_9H_9IO_2$	
19	$C_{10}H_{16}$	
20	$C_{10}H_7I$	
21	$C_7H_4IF_3$	
22	$C_{11}H_{13}F_3$	
23	$C_6H_5NO_2$	
24	$C_7H_4IF_3$	
25	C_5H_4IN	
26	C_7H_7I	
27	$C_6H_4INO_2$	
28	$C_{10}H_{13}NO_2$	

Negishi cross-couplings involving *ortho*-coordinating electrophiles and other substitution patterns: GCs




Signal
h
g
f
e
6
6
14
15
9
17
18
20
13
9
1
2
4
16
19
19
2
4
6
8
10
12
Running Time (min)
N,N-Diethyl-2-iodobenzamide + n-C$_4$H$_9$Zn
N,N-Diethyl-2-iodobenzamide + BnZn
Methyl-2-iodobenzoate + n-C$_4$H$_9$Zn
Methyl-2-iodobenzoate + BnZn


Signal
l
k
j
i
6
9
26
25
27
28
1
2
4
24
22
23
9
21
4
2
4
6
8
10
12
14
16
18
Running Time (min)
1-Iodo-2-(methoxymethyl)benzene + n-C$_4$H$_9$Zn
1-Iodo-2-(methoxymethyl)benzene + BnZn
2-Iodobenzanilide + n-C$_4$H$_9$Zn
2-Iodobenzanilide + BnZn


2-Iodoacetophenone + n-C$_4$H$_9$Zn
2-Iodoacetophenone + BnZn
Signal
n
m
6
31
6
32
9
29
1
2
4
30
30
2
4
6
8
10
Running Time (min)

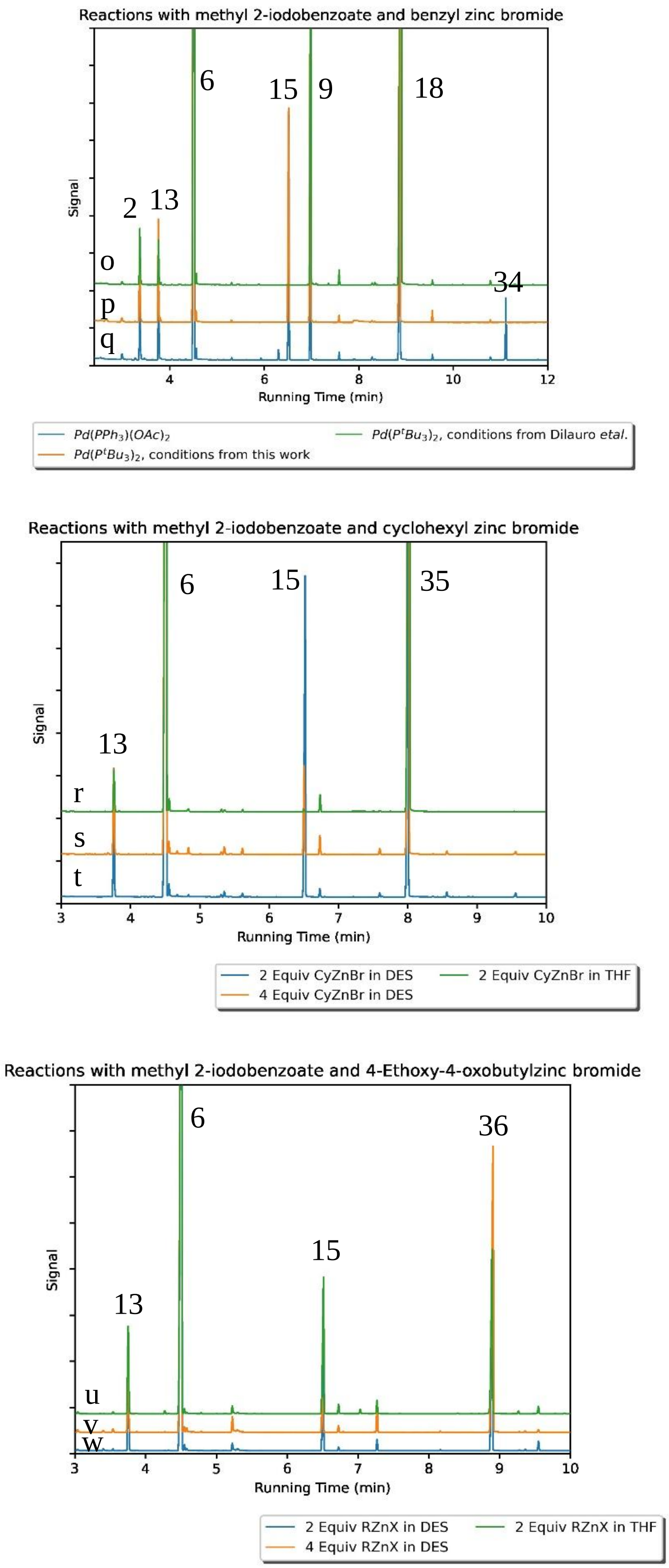
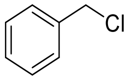
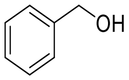
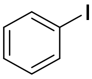
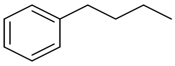
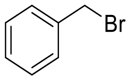
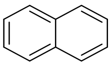
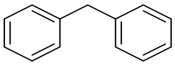
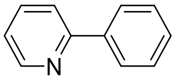
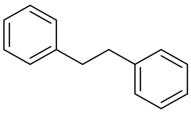
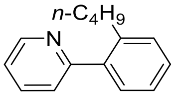
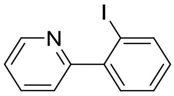
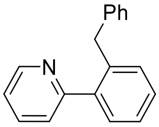
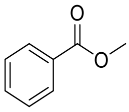
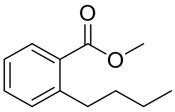
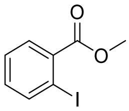
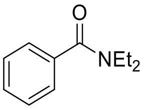
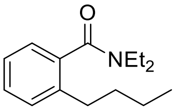
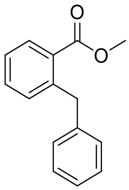
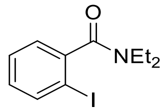
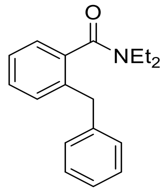
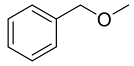
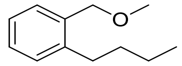
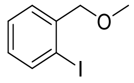
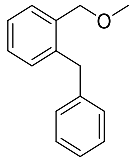
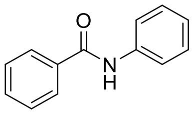
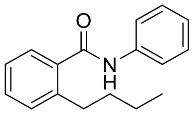
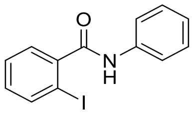
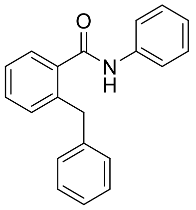
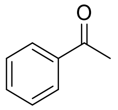
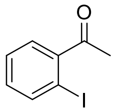
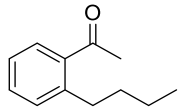
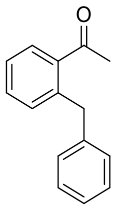
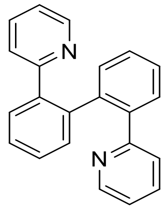
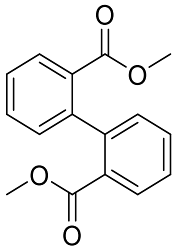
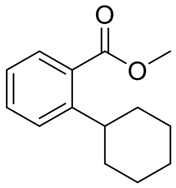
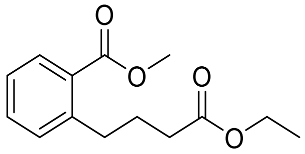


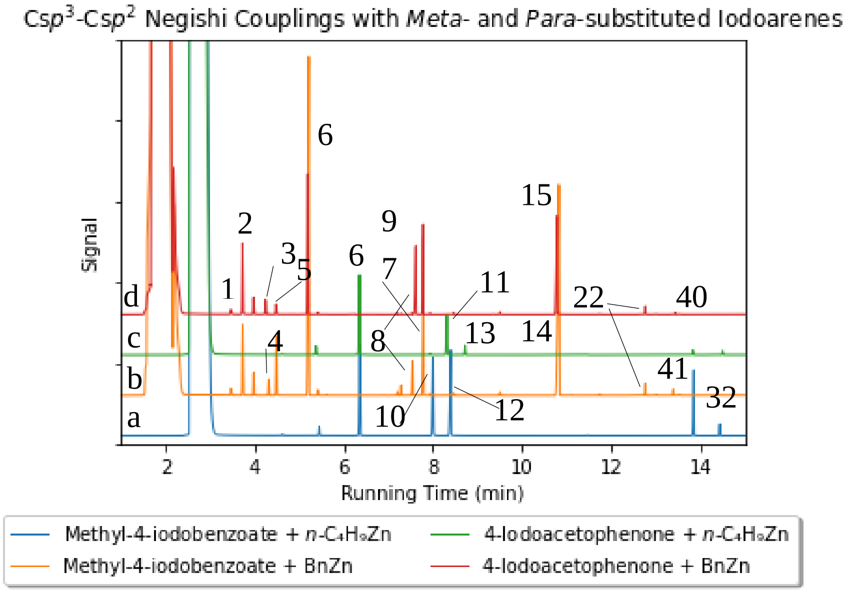
Figure S20: GC chromatograms from the reactions between iodobenzene & ortho-substituted iodoarenes with organozinc reagents. Experiments a, b, c ,d, e, g, h, m, n, o, p, q, r, s, t, u, v, w were run in the DB5 column; f, i, j, k, l & n in the Rix-17 column. The structure associated to the peaks is outlined in Table S16.

Table S16: Chemical structure of the compounds associated to the chromatograms plotted in Figure S20.

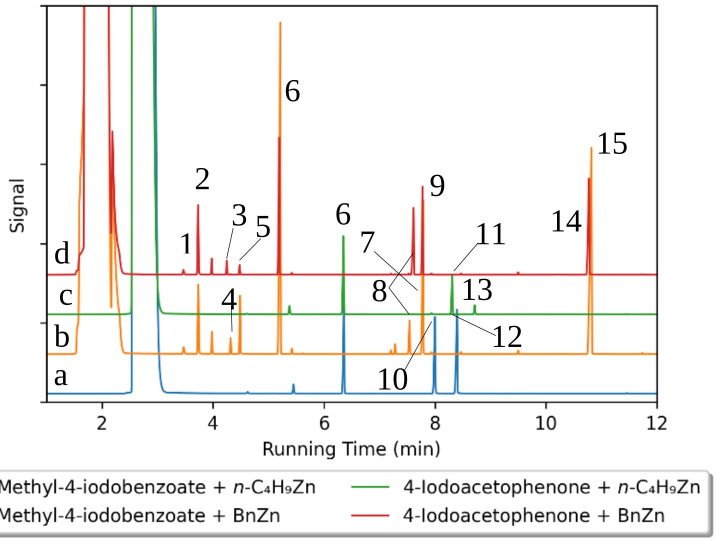
GC Peak	Formula	Structure
1	C_7H_7Cl	
2	C_7H_8OH	
3	C_6H_5I	
4	$C_{10}H_{14}$	
5	C_7H_7Br	
6	$C_{10}H_8$	
7	$C_{13}H_{12}$	
8	$C_{11}H_9N$	
9	$C_{14}H_{14}$	
10	$C_{15}H_{17}N$	
11	$C_{11}H_8IN$	
12	$C_8H_{15}N$	
13	$C_8H_8O_2$	
14	$C_{12}H_{16}O_2$	
15	$C_8H_7IO_2$	
16	$C_8H_{15}NO$	
17	$C_{15}H_{23}NO$	
18	$C_{15}H_{14}O_2$	

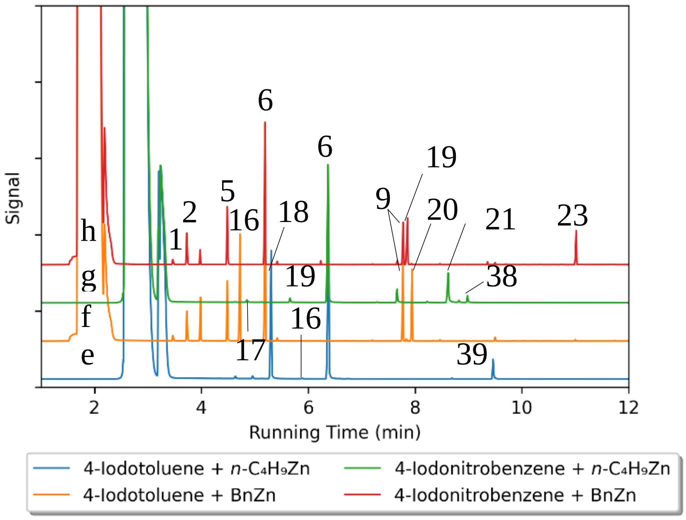
19	$C_{11}H_{14}INO$	
20	$C_{18}H_{21}NO$	
21	$C_{8}H_{10}O$	
22	$C_{12}H_{18}O$	
23	$C_{8}H_{9}IO$	
24	$C_{15}H_{16}O$	
25	$C_{13}H_{11}NO$	
26	$C_{17}H_{19}NO$	
27	$C_{13}H_{10}INO$	
28	$C_{20}H_{17}NO$	
29	$C_{8}H_{8}O$	
30	$C_{8}H_{7}IO$	
31	$C_{12}H_{16}O$	
32	$C_{12}H_{16}O$	

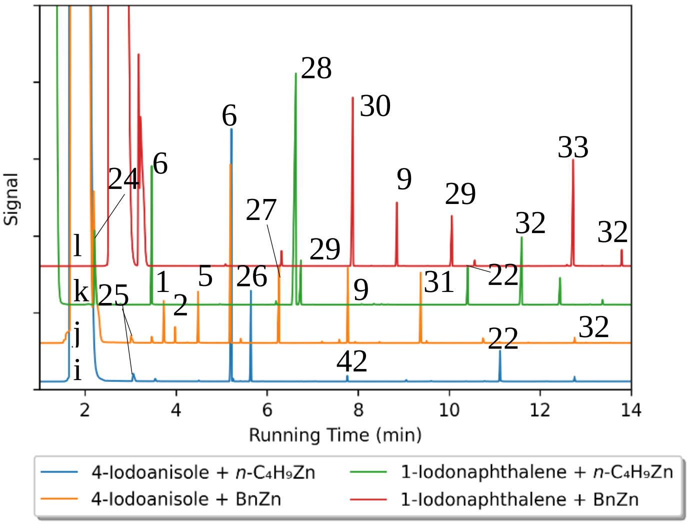
33	$C_{22}H_{16}N_2$	
34	$C_{16}H_{14}O_4$	
35	$C_{14}H_{18}O_2$	
36	$C_{14}H_{18}O_4$	



Csp^3-Csp^2 Negishi Couplings with *Meta*- and *Para*-substituted Iodoarenes







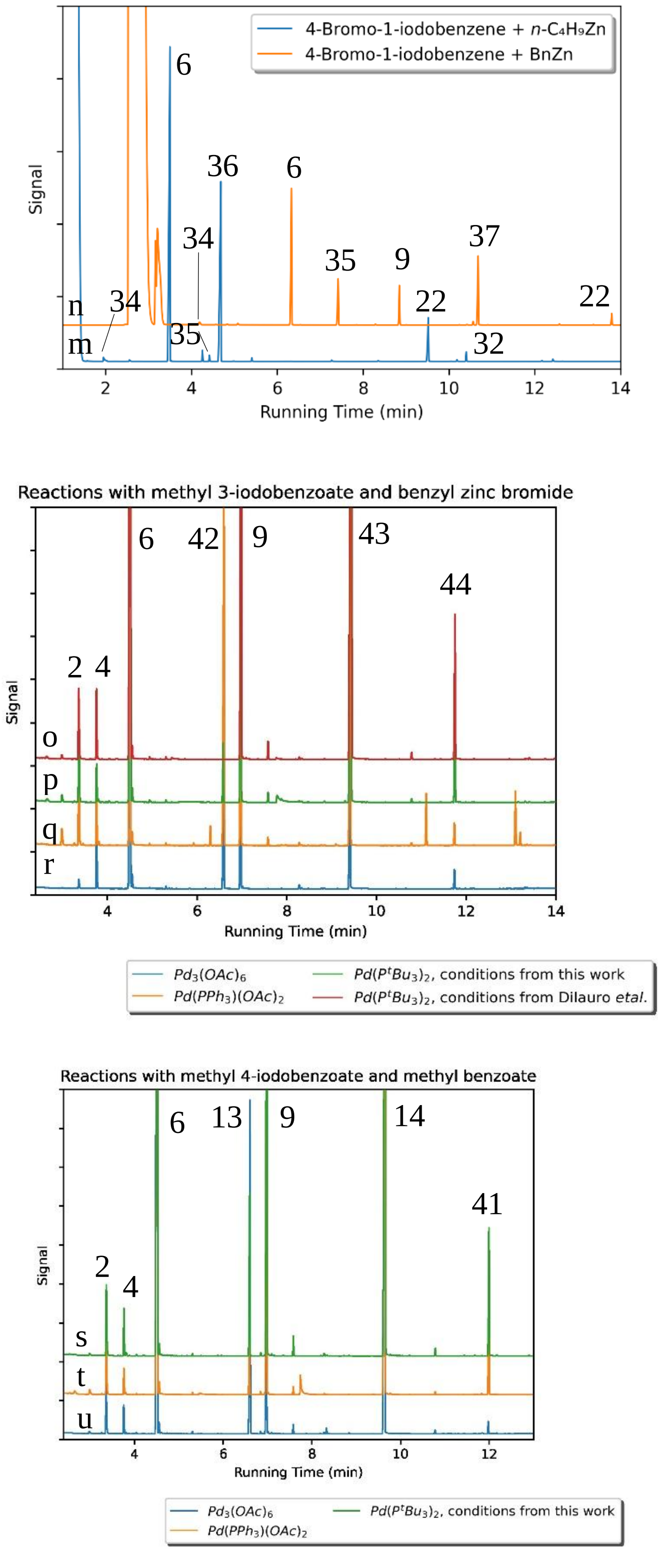
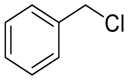
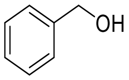
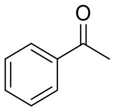
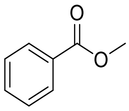
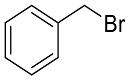
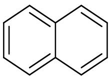
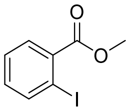
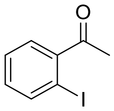
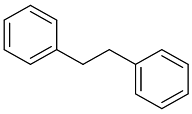
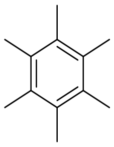
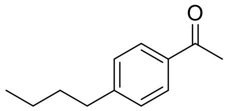
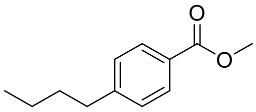
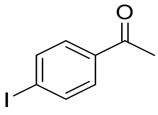
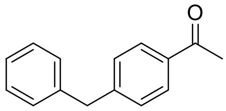
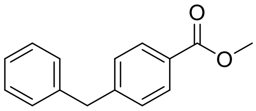
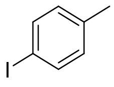
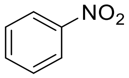
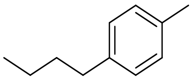
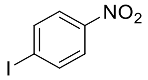
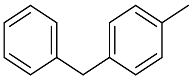
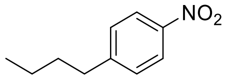
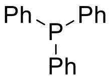
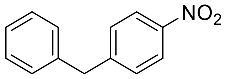
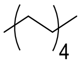
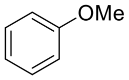
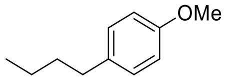
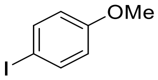
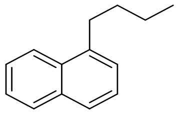
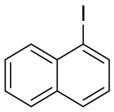
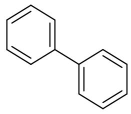
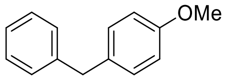
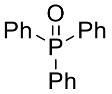
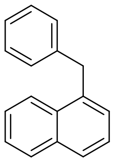
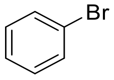
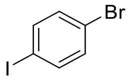
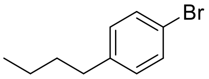
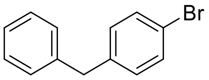
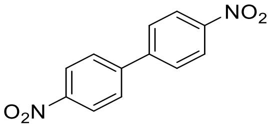
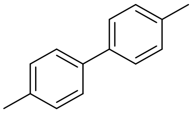
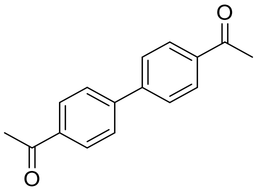
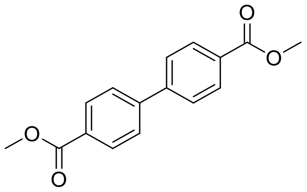
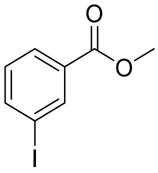
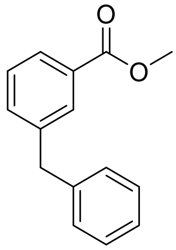
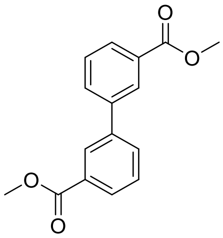


Figure S19: GC chromatograms from the reactions between *para* and *meta*-substituted iodoarenes with organozinc reagents. Experiments a, b, c ,d, e, f, g, h, i, j, l & n, o, p, q, r, s, t, u were run in the Rix-17 column; k & m in the DB5 column. The structure associated to the peaks is outlined in Table S17.

Table S17: Chemical structure of the compounds associated to the chromatograms plotted in Figure S19.

GC Peak	Formula	Structure
1	C_7H_7Cl	
2	C_7H_8OH	
3	C_8H_8O	
4	$C_8H_8O_2$	
5	C_7H_7Br	
6	$C_{10}H_8$	
7	$C_8H_7IO_2$	
8	C_8H_7IO	
9	$C_{14}H_{14}$	
10	$C_{12}H_{18}$	
11	$C_{12}H_{16}O$	
12	$C_{12}H_{16}O_2$	
13	C_8H_7IO	
14	$C_{15}H_{14}O$	
15	$C_{15}H_{14}O_2$	
16	C_7H_7I	
17	$C_6H_5NO_2$	

18	$C_{11}H_{16}$	
19	$C_6H_4INO_2$	
20	$C_{14}H_{14}$	
21	$C_{10}H_{13}NO_2$	
22	$C_{18}H_{15}P$	
23	$C_{13}H_{11}NO_2$	
24	$C_{10}H_{22}$	
25	C_7H_8O	
26	$C_{11}H_{16}O$	
27	C_7H_7IO	
28	$C_{14}H_{16}$	
29	$C_{10}H_7I$	
30	$C_{12}H_{10}$	
31	$C_{14}H_{14}O$	
32	$C_{18}H_{15}OP$	
33	$C_{17}H_{14}$	
34	C_6H_5Br	
35	C_6H_4IBr	
36	$C_{10}H_{13}Br$	
37	$C_{13}H_{11}Br$	
38	$C_{12}H_8N_2O_4$	

39	$C_{10}H_{14}$	
40	$C_{16}H_{14}O_2$	
41	$C_{16}H_{14}O_4$	
42	$C_8H_7IO_2$	
43	$C_{15}H_{14}O$	
44	$C_{16}H_{14}O_4$	

Negishi coupling between 2-phenylpalladacycle and benzyl zinc in DES: GC's

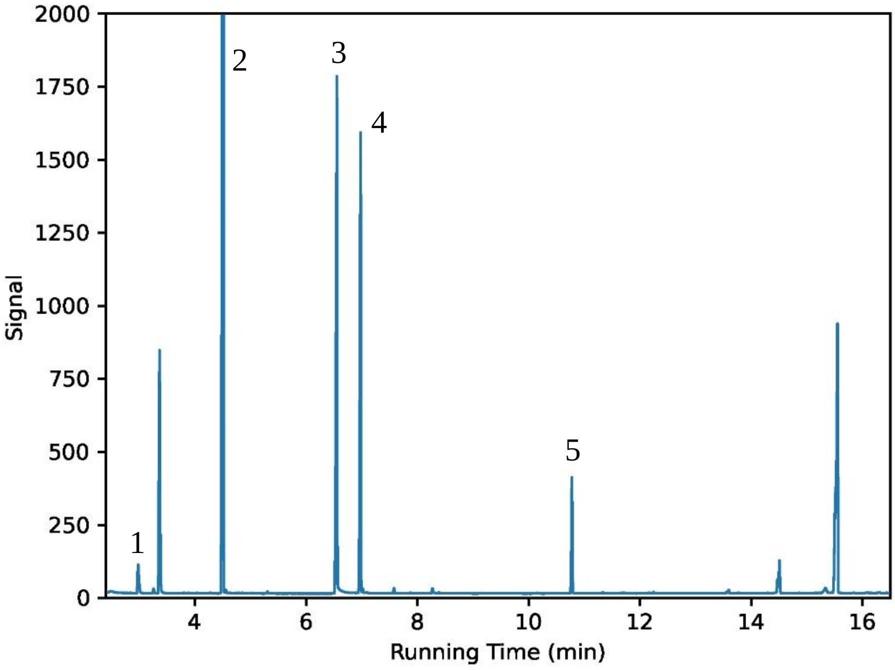
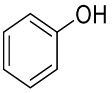
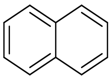
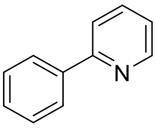
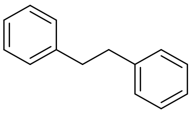
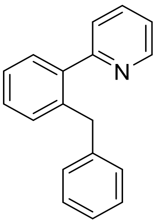


Figure S22: GC chromatogram from the reaction between 2-phenylpyridine palladacycle and benzyl zinc in DES. The Experiment was run in a DB-5 column. The structure associated to the peak numbers is outlines in Table S18.

Table S18: Chemical structure of the compounds associated to the chromatograms plotted in Figure S22.

GC Peak	Formula	Structure
1	C_6H_6O	
2	$C_{10}H_8$	
3	$C_{11}H_9N$	
4	$C_{14}H_{14}$	
5	$C_{18}H_{15}N$	

Negishi coupling between methyl 2,5-diiodobenzoate and benzyl zinc in DES: GC's

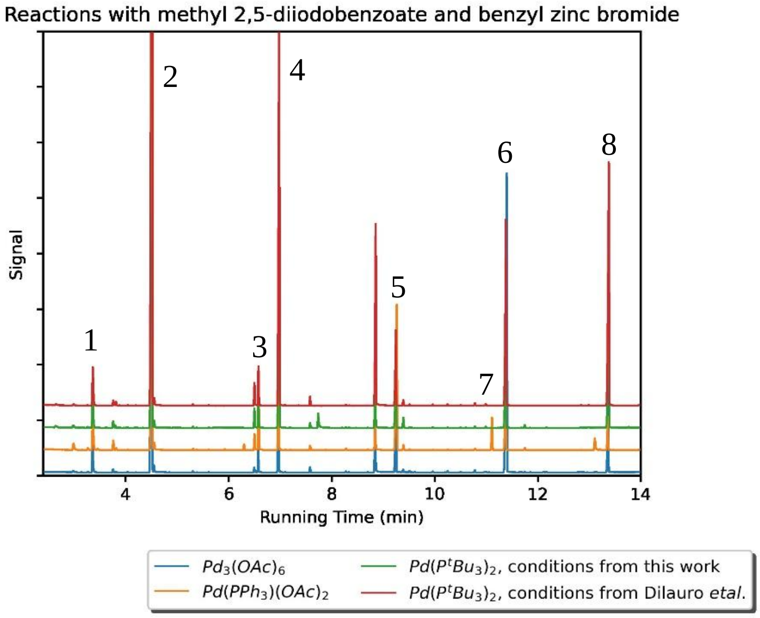
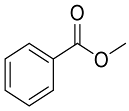
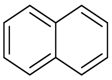
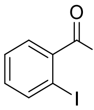
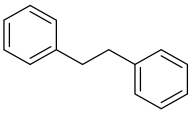
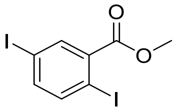
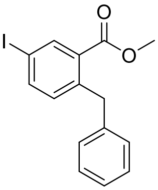
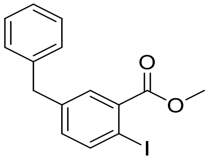
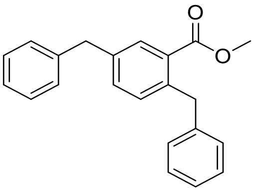


Figure S23: GC chromatogram from the reaction between methyl 2,5 diiodobenzoate and benzyl zinc in DES. The Experiment was run in a DB-5 column. The structure associated to the peak numbers is outlines in Table S19.

Table S19: Chemical structure of the compounds associated to the chromatograms plotted in Figure S23.

GC Peak	Formula	Structure
1	$C_8H_8O_2$	
2	$C_{10}H_8$	
3	$C_8H_7IO_2$	 or isomer
4	$C_{14}H_{14}$	
5	$C_8H_8I_2O_2$	
6	$C_{15}H_{13}IO_2$	

7	$C_{15}H_{13}IO_2$	
8	$C_{22}H_{19}IO_2$	

Negishi coupling between methyl 2,3,5-triiodobenzoate and benzyl zinc in DES: GC's

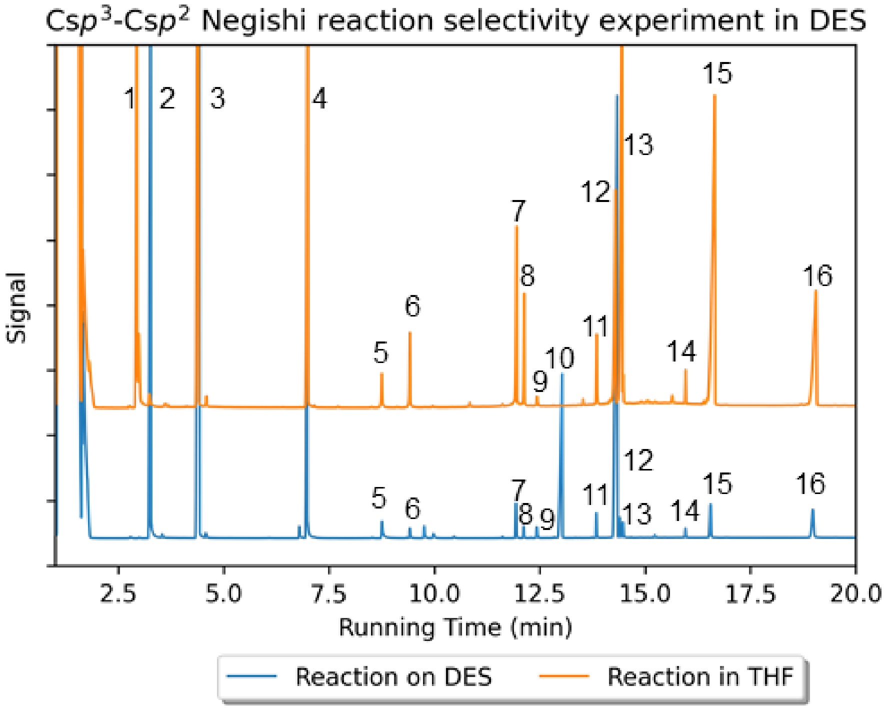


Figure S24: GC chromatogram from the reaction between methyl 2,3,5 triiodobenzoate and benzyl zinc catalysed by Pd acetate. The Experiment was run in a Rix-17 column. The structure associated to the peak numbers is outlines in Table S20.

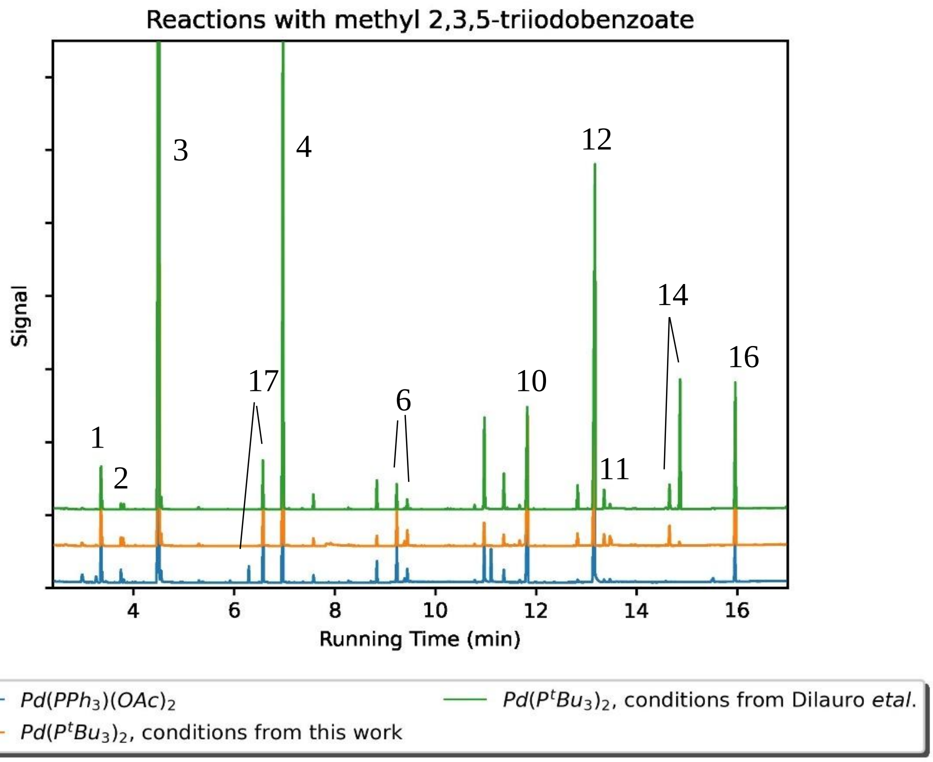
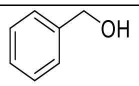
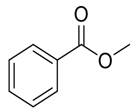
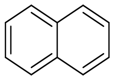
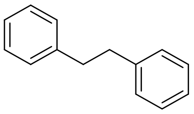
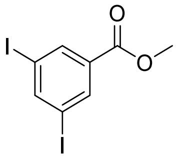
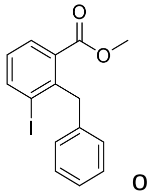
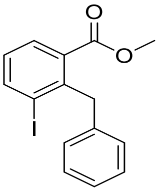
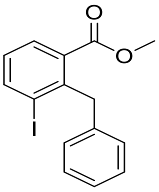
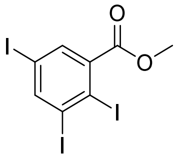
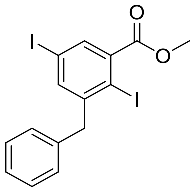
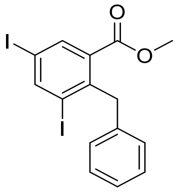
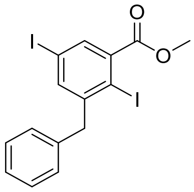
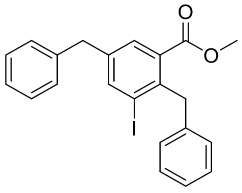
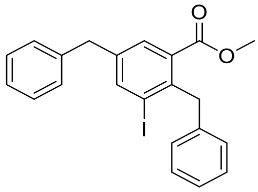
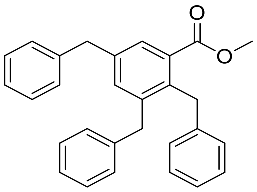
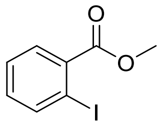


Figure S25: GC chromatogram from the reaction between methyl 2,3,5 triiodobenzoate and benzyl zinc in DES. The Experiment was run in a DB-5 column. The structure associated to the peak numbers is outlines in Table S20.

Table S20: Chemical structure of the compounds associated to the chromatograms plotted in Figure S24 and S25.

GC Peak	Formula	Structure
1	C_7H_8OH	
2	$C_8H_8O_2$	
3	$C_{10}H_8$	
4	$C_{14}H_{14}$	
6	$C_8H_8I_2O_2$	 or isomers
7	$C_{15}H_{13}IO_2$	 or isomers

8	$C_{15}H_{13}IO_2$	 or isomers
9	$C_{15}H_{13}IO_2$	 or isomers
10	$C_8H_5I_3O_2$	
11	$C_{15}H_{12}I_2O_2$	 or isomer
12	$C_{15}H_{12}I_2O_2$	
13	$C_{15}H_{12}I_2O_2$	 or isomer
14	$C_{22}H_{19}IO_2$	 or isomer
15	$C_{22}H_{19}IO_2$	 or isomer
16	$C_{29}H_{26}O_2$	
17	$C_8H_7IO_2$	 or isomer

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